Proceedings of the Second International Consensus Meeting on Musculoskeletal Infection

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This document on the prevention, diagnosis and treatment of orthopaedic infections is compiled as a result of work of over 800 individuals from around the globe. It is important to note that the text for each question has been composed by individual experts in each field. It is certainly possible that key studies have been overlooked, some points may be emphasized more than other points and each section may suffer from potential individual biases. Nevertheless, the responses to each question have been scholarly researched, evaluated by the majority of the delegates and discussed and voted on during the face-to-face meeting in Philadelphia.

It is important to note that each section does not necessarily represent the personal opinions of Drs. Parvizi and Gehrke, or any individual participating in the Consensus. Therefore, the document should not be interpreted as definitive or in fact represent the "standard of care." The experts who committed innumerable hours to generate this document have done so in the hopes of improving patient care.

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Orthopaedic Research and Education Foundation
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publication of the consensus material.

Foreword

The English dictionary defines consensus as a "general agreement about something." It is seen as the middle ground in decision-making, between total assent and total disagreement. The process of consensus depends on the participants having shared values and common goals. A consensus leads to the generation of an agreement on specific issues that provide overall direction for the future. The Second International Consensus Meeting (ICM) on orthopaedic infections had the above objectives in mind. The second meeting was built on the success of the first ICM meeting that was held in 2013 and implemented additional steps, based on the input of the delegates from the prior meeting, with the intention of improving the outcomes.The second ICM meeting was different in three aspects:

1) It included delegates from all subspecialties of orthopaedics including: Hip and Knee Arthroplasty; Foot and Ankle; Oncology; Pediatrics; Shoulder; Elbow; Spine; Sports; and Trauma.
2) The consensus was conducted according to the Delphi method again (see below). However, this time instead of having a central group conduct the research and write out the recommendations and rationale for each question, individual delegates were engaged. For each question, the delegates evaluated the available literature, extracted the evidence for current practices and identified the areas in need of further research. The level of evidence related to each "recommendation" was also identified. To the best of our knowledge, no published work related to orthopaedic infections was missed.
3) The meeting allowed for the participation of representatives from governmental organizations, payers and business administrations. Although these participants were not allowed to vote in the process, their presence was deemed to be important in developing the road map for funding, supporting and approving technologies related to orthopaedic infections in the future.

The name Delphi derives from the Oracle of Delphi and was developed in the beginning of the Cold War to forecast the impact of technology on warfare. General Henry H. Arnold had ordered the creation of a report for the United States Army Air Corps on technological capabilities that could be used in future warfare. Very soon it became apparent that forecasting methods, technological approaches and quantitative models could not be used, as little "scientific evidence" had been published in this field. To overcome these limitations, the Delphi method was developed by Project RAND during the 1950s and 1960s [1]. The Delphi method continues to be used by the military today and has found its way into the scientific and medical communities [2].

The exact description of the Delphi method that was utilized in the first ICM meeting has been previously published [3] and the document or executive summaries have been published in various venues [4–6]. The second ICM meeting also followed similar steps, with every step of the process being supervised by Dr. William Cats-Baril. The seed for the second consensus meeting was set in soil in June of 2016 when, at the request of many experts from around the world, we decided to proceed. Thirteen specific steps were followed.

Step 1 (August 2016 to December 2016): **Selection of Delegates.** This step aimed to gather the experts from around the globe, with no country overlooked, who could lend their expertise to the consensus process. The delegates were identified based on their publication track record in the field (at least five publications within the last five years), specialty society nominations or their clinical expertise (high volume) in taking care of patients with orthopaedic infections. The search identifed 953 delegates who were sent invitations. Some of the delegates did not respond to the invitation (63) or declined to participate (21), leaving 869 potential delegates to participate.

Step 2 (December 2016 to April 2017): **Identification of Issues.** The delegates were then asked to send in 5 to 10 questions (issues) in the field of orthopaedic infections that they felt needed to be explored. A total of 3,210 questions were received.

Step 3 (April 2017 to August 2017): **Ranking of Questions.** The collected questions were then sent to the delegates again and they were asked to prioritize them. In this process, we did not deliberately remove duplicate questions and did not make any changes to the "writing" of the questions. We believed that "duplications" perhaps represented the higher priority of a question.

Step 4 (August 2017 to November 2017): **Evaluation of Ranked Questions.** Once the ranking had been received, the duplicate questions were removed, and the stem of each question was rewritten according to the Delphi method. This step was necessary to remove "suggestive" phrases such as "what is the role of…?" as opposed to "is there a role…?" This left us with 652 questions that comprised the final set of questions to be explored.

Step 5 (December 2017): **Assignment of Questions.** The final set of questions were then assigned to at least two delegates per question based on the publication track record of the delegate or the desire of a delegate to research a specific question. The delegates were given specific instructions on how to conduct research on the topics presented in each question and how to write up the responses.

Step 6 (December 2017 to March 2018): **Systematic Review.** During this time period, the delegates were actively engaged in researching a specific question and preparing the preliminary document related to each question. The two delegates assigned to each question worked independently for all orthopaedic specialties except for the Shoulder group who decided to work together. No published works in the English language were meant to be missed during this process.

Step 7 (February 2018 to April 2018): **Interdelegate Discussions.** The document received from one delegate was then sent to the other and both delegates were made aware of each other's write up and research. The activity was coordinated centrally to create one document that was acceptable by both delegates. Over 6,000 emails were exchanged during this process alone.

Step 8 (April 2018 to May 2018):**Document Merging/Editing.** All received documents were reviewed, write-ups checked to remove plagiarism, references updated and the English language edited.
Step 9 (June 2018 to July 2018): **Document Evaluation by all Delegates.** Although the documents generated were posted on the website (www.ICMPhilly.com) for many months and available for view by EVERYONE (including the public), the final document was sent to the delegates and they were asked to review any and all questions that were posted live on the website. We received numerous comments from delegates during this period and implemented any and all appropriate changes to the document prior to the meeting.

Step 10 (July 2018): **Final Pre-Meeting Review/Editing.** The entire document was reviewed by the internal editorial team and some additional changes were made. The latest publications, up until June 30, 2018, were also checked and added to relevant sections.

Step 11 (July 25–26, 2018): **Pre-Vote Discussion.** All delegates who traveled to Philadelphia met in their workgroups and discussed some of the questions in their fields. The questions were divided into four categories: 1) Highly clinically relevant with little evidence supporting the recommendation; 2) Highly controversial and clinically relevant; 3) Highly relevant and with great supportive evidence for the recommendation; and 4) Not clinically highly relevant with or without supportive evidence. During the meeting, questions from categories 1 and 2 were discussed.

Step 12 (July 27, 2018). **Voting.** All questions were presented on a screen and the delegates were allowed to vote in real time. The result from voting appeared on the screen shortly after the vote. There were three possible responses to each recommendation: agree; disagree; or abstain. The process of voting was clearly explained by Dr. William Cats-Baril to the delegates prior to voting.

Step 13 (August 2018 onwards): **Dissemination of Consensus Document.** Following the meeting, the voting results were implemented into the document. The document was additionally reviewed by outside editors of Journals, in particular by Dr. Michael A. Mont and his fellow, Dr. Nipun Sodhi, Dr. Thomas Bauer and Dr. Adolph J. "Chick" Yates. The delegates were given the opportunity to review the final document over a four-week period and to provide any additional feedback. All suggested and appropriate changes were implemented into the document. The final document was then sent to various journals for publication as well as for publication in a consolidated book form. The final document is also being translated into different languages.

As can be seen from the above, the delegates were very engaged at every step of the way in generating the consensus document. It is clear, however, that a complex process, like the above, may fall victim to some shortcomings and errors. We made every effort to minimize those as much as possible. We also attempted to be inclusive of all experts from around the world. We are certain that we may have missed some very deserving experts who should have been part of this process. We apologize in advance to any experts who were missed, to the readers who may have to endure some errors in the document, to the authors of reports who may have been missed unintentionally and to anyone else who may feel perturbed because of our shortcomings. We hope that the document that is generated will serve the orthopaedic community for years to come and improve the care of our patients.

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Acknowledgments

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Editorial Board

Special thanks to Dr. Michael A. Mont and his fellow, Dr Nipun Sodhi, who read through the entire document after the July meeting, investing numerous hours editing and checking for accuracy and completeness. We are truly grateful to both of them. Our gratitude also goes out to Dr. Thomas Bauer and Dr. Adolph J. "Chick" Yates, who also spent many hours reading and editing the post-vote document.

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PART I

GENERAL ASSEMBLY

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Prevention

1.1. PREVENTION: HOST RELATED, LOCAL FACTORS

Authors: Hao Shen, Peter Thomas, Qiaojie Wang

QUESTION 1: Does the presence of skin lesions (i.e., boils, grazes, folliculitis, etc.), either in the proximity or distant to the surgical site, predispose patients to surgical site infections/periprosthetic joint infections (SSIs/PJIs)? If so, is it necessary for patients with these skin lesions to undergo treatment prior to elective total joint arthroplasty (TJA)?

RECOMMENDATION: The presence of active skin infections, either in the proximity or distant to the surgical site, can potentially increase the risk of SSIs/PJIs in patients undergoing elective TJA. Therefore, surgery should be delayed until these lesions are treated and/or resolved. Placing surgical incisions through eczematous or psoriatic lesions should be avoided as well, whenever possible.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 3%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

Optimization of the host is effective in minimizing the risk of PJIs/SSIs prior to elective total joint arthroplasty.

Presence of Active Infection

Bacterial Infection

For most SSIs after total hip and knee arthroplasties, the source of pathogens is the endogenous flora of the patient's skin [1,2]. The presence of bacterial infection of the skin, such as boils, folliculitis and erysipelas, is encountered in patients undergoing total hip and knee arthroplasty, although the incidence is not clear.

Folliculitis is most commonly caused by *Staphylococcus aureus* in all geographic regions, according to an international survey [3]. Nasal carriage of *S. aureus* was found in 58% of patients with folliculitis/furuncles overall and was associated with chronic furunculosis [4]. There is a concern that the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) is increasing for these patients, with the overall MRSA rate in the skin and subcutaneous tissue infections reaching as high as 36% in North America [3].

Erysipelas affects predominantly adult patients in the sixth or seventh decade, a similar demographic to those considered for total joint arthroplasty, and occurs on the lower limb in more than 80% of cases. It is often caused by the disruption of the cutaneous barrier (e.g., leg ulcer, wound, fissured toe-web intertrigo, pressure ulcer), lymphedema, chronic edema or local surgical operations. The condition is most commonly caused by β-hemolytic streptococci of group A, less so by group B, C or G streptococci and rarely by staphylococci [5]. Impetigo consists of discrete purulent lesions that are nearly always caused by β-hemolytic streptococci and/or *S. aureus*. Resistance to fusidic acid in the European strains of *S. aureus* causing impetigo has increased in recent years [6]. MRSA is a major nosocomial pathogen that may also cause impetigo [7].

As the causative organisms for these bacterial skin infections are also common pathogens in SSIs/PJIs following TJAs [8–11], if such skin lesions are in the proximity of the surgical site, the risk of SSIs/PJIs could potentially increase.

These bacterial skin infections may also have some risk of bacteremia [12]. Although it is well-accepted that seeding of the operative site from a distant focus of infection can be a source of SSI pathogens [13], literature regarding the impact of remote skin infection on SSIs from a clean wound is scarce. In a retrospective study [14] on 2,349 patients with clean surgical wounds, the wound infection rate in the 53 patients with remote skin infections was 20.7% compared to the 6.9% in the 2,141 patients without remote infections ($p < 0.001$). It should be noted that most of the procedures in that study were not orthopaedic procedures. Theoretically, for patients who have a prosthesis or other implant placed during the operation, such a remote seeding could be particularly important because such devices provide a nidus for attachment of organisms [15].

Fungal Infection

Dermatophytosis (i.e., tinea) of the feet and inguinal area is not only contaminated by bacteria, but also can be a portal of entry for bacteria through rhagade [12,16]. If it is in the proximity of incisions, there might be the risk of contaminating the tissue in the surgical wound [17]. PJI with fungal pathogens is a rare but challenging clinical problem [18]. Therefore, elective TJA should not be performed until these infections are eradicated, no matter whether they are in proximity of or distant from the surgical site.

Special attention should be paid to *Cutibacterium acnes* (*C. acnes*) (formerly *Propionibacterium acnes*). This organism is not only found in facial acne lesions but also on the trunk. Skin areas rich in sebaceous glands are a particular risk for *C. acnes* surgical site infections [19]. In shoulder arthroplasty, a higher incidence of *C. acnes* inducing periprosthetic joint infections have been reported [20–22] and routine local preoperative treatments have been described as not being sufficient in reducing *C. acnes* loading [23]. New strategies like preoperative use of benzoyl peroxide (known from topical therapy

for acne vulgaris) have proven to be effective in reducing the risk of infection by *C. acnes* [24,25].

Skin Disorders with the Potential for Enhanced Microbial Load

There are no existing studies evaluating the risk of SSIs when incisions are placed through eczematous or psoriatic lesions. Psoriatic plaques have been shown to harbor increased concentrations of bacteria compared with unaffected skin, causing concern for an increased risk of infection [26,27]. However, some studies have demonstrated that there is no such association [28,29].

Patients with atopic dermatitis have higher levels of bacterial colonization on both the affected and normal skin [30,31]. In nonaffected normal skin, *S. aureus* colonization was found in 19 of 30 (63%) atopic dermatitis patients compared with 6 of 25 (24%) in nonatopic eczema patients and 1 of 30 (3%) in the healthy control group, respectively ($p < 0.05$) [32]. That means that even when the incision is made in the normal skin, the risk of implant infection remains high, as the normal skin of atopic dermatitis patients is more heavily colonized than the skin of healthy patients. Lim et al. reported two cases of PJI related to remote atopic dermatitis [33].

The degree of *S. aureus* colonization may also depend on the severity and duration of the eczematous lesions. The colonization rates in acute and chronic skin lesions of patients with atopic dermatitis are significantly different, with a colonization rate of more than 70% in acute lesions and about 30% in chronic lesions [34,35].

Therefore, patients with active skin disease should see their dermatologist preoperatively, and every attempt should be made to manage skin plaques before surgery to decrease bacterial burden. Placing surgical incisions through eczematous or psoriatic lesions should be avoided if possible.

Ulcerations

Venous leg ulcers and diabetic foot ulcers usually have bacterial contamination and might be a source of systemic bacterial spread [36,37]. In general, ulceration of the skin (including neoplasm) is a substantial risk factor for surgical site infections [38]. It was recommended that elective arthroplasty not be carried out in patients with active skin ulcerations (active ulcerations being defined as breaks in the skin barrier, excluding superficial scratches) [39].

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QUESTION 2: Does poor dental hygiene increase the risk of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)? If yes, is there a role for obtaining dental clearance in patients with poor dental hygiene to reduce the risk of SSI/PJI?

RECOMMENDATION: There is a small yet real risk of hematogenous spread of oral pathogens to patients undergoing arthroplasty. Patients with poor oral hygiene undergoing arthroplasty are at increased risk of subsequent SSI/PJI. Therefore, patients with oral disease and poor dentition should be identified and optimized prior to elective arthroplasty.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 5%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Transient bacteremia occurs following everyday activities such as tooth-brushing and flossing, as well as following dental procedures [1–4]. Associated with this transient bacteremia is the theoretical risk of hematologic spread, seeding of the prosthesis, and subsequent development of a PJI. Multiple small-scale studies have shown an association between bacteria isolated in PJI and oral flora [5–11].

With this in mind, in the past many joint arthroplasty surgeons have advocated for routine dental screening prior to total joint arthroplasty (TJA). In spite of this theoretical risk, controversy exists regarding the relationship of dental pathology and dental procedures and the development of PJIs. There have been several large-scale studies that have not identified an association between dental procedures and the development of PJI. One example is a prospective case-control study that showed that there was no increased risk of PJI in patients who underwent dental procedures following TJA [12]. Furthermore, antibiotic prophylaxis did not decrease the risk of PJIs [12]. In an additional case-control study by Skaar et al., using the Medicare Current Beneficiary Survey data, the group demonstrated that there were no associations between dental procedures and the subsequent development of PJIs. This was true for patients who underwent both high and low-risk procedures [13]. In a large retrospective review of a national health registry, Kao et al. identified 57,066 patients who underwent TJA and had dental procedures postoperatively. They matched these patients with those who had not undergone dental procedures. The authors found no significant difference in the rate of PJIs between the two groups [14]. In 2014, Lampley et al. compared the incidence of PJI between elective TJA patients who underwent dental screening prior to surgery to hip fracture patients treated with total hip arthroplasty (THA) or hemiarthroplasty who did not undergo dental screening. The authors found no significant difference in development PJI between the two groups [15].

In spite of the above evidence, a rare risk for hematogenous spread of PJI persists in a small subset of patients [7,11]. In a study by Bartzokas et al., the authors identified four cases of PJI where an oral pathogen was associated with poor dental hygiene [6]. This is supported by the fact that the incidence of bacteremia following dental procedures is higher in those patients who have dental pathology and poor dental hygiene [16,17]. Given this relatively small risk, several studies have sought to identify the prevalence of dental pathology in the TJA population. In a 2011 study by Barrinngton and Barrington, 23% of patients undergoing TJA were found to have dental pathology [18]. However, in a 2014 study, Takarski et al. identified 12% of patients having dental pathology at screening visits prior to TJA. Furthermore, the authors used multivariate analysis to identify six risk factors for failing dental clearance. Those risk factors were narcotic use, tobacco use, not having visited a dentist within 12 months, history of pulled teeth, older age and flossing less than once daily [19].

Given the lack of evidence linking dental pathology and procedures to hematogenous spread and subsequent development of PJI, it may be reasonable to require dental screening only for high-risks patients with specific risk factors for dental pathology. While recent studies have shed light on the risk factors associated with discovering dental pathology, further studies are needed to identify which patients should undergo dental screening following TJA.

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QUESTION 3: Should routine dental clearance be obtained prior to total joint arthroplasty (hip/knee/shoulder/ankle)?

RECOMMENDATION: No. While dental pathology has been reported in a subset of patients undergoing joint arthroplasty, there are no prospective controlled studies supporting the role of pre-surgical dental clearance in reducing the rates of subsequent periprosthetic joint infections (PJIs).

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 76%, Disagree: 17%, Abstain:7% (Super Majority, Strong Consensus)

RATIONALE

Evidence that demonstrates a relationship between dental disease and the risk for subsequent surgical site infections (SSIs) and PJIs is limited. It is known that the presence of bacteria in the bloodstream is common after any dental treatment [1–4], and this has also been associated with oral activities of daily life, such as chewing, teeth brushing or flossing [1,2]. Even so, the bacterial inoculum necessary to cause a clinically important bacterial infection in humans is unknown [2].

A few case reports in the literature have attempted to link PJI with a dental source [5–16]. Such case reports document PJI associated with a recent dental procedure and with an organism that is reasonably associated with oral flora. A logical extension of this association of PJI with an oral source has led to the practice of addressing dental concerns prior to arthroplasty surgery with the expectation that this could perhaps decrease the postoperative occurrence of dental-associated PJIs. While perhaps logical, there is little published literature to support this practice. Two studies have documented dental pathology in 12 to 23% of patients planning to undergo hip or knee arthroplasty [17,18]. Other reports show a prevalence of between 30 and 50% of dental pathology in elderly patients in the United States [2,17], with 23% of adults having untreated caries, with the incidence increasing in certain groups such as the institutionalized elderly, smokers, drinkers of carbonated beverages, patients with chronic conditions such as diabetes or rheumatic diseases and in those at a lower socioeconomic level [17].

It has been suggested that the need for dental clearance could perhaps be limited to this smaller percentage of patients who could potentially be identified by a preoperative questionnaire [18]. The American Academy of Orthopaedic Surgeons (AAOS) and the American Dental Association (ADA) have published numerous guidelines in the past [19–21] regarding antibiotic prophylaxis prior to dental procedures for prosthetic joint implant patients, but little has been said about preoperative dental clearance prior to joint arthroplasty. Only one study has compared the incidence of PJIs in a population of patients who underwent dental clearance prior to arthroplasty with a population of arthroplasty patients who had no such clearance [22]. This latter group of patients was not a prospective matched control cohort, but rather was composed of hip fracture patients treated with non-elective arthroplasty. This study was not only limited by the lack of a true control group, but also by the relatively small number of patients. Nevertheless, the conclusion of this study was that dental clearance prior to arthroplasty did not provide a significant decrease in PJIs.

In the absence of concrete data, we believe that routine dental clearance prior to joint arthroplasty is not mandated. We recognize that patients with active oral disease or infection may be at higher risk for subsequent SSI/PJIs, and every effort should be made to identify these patients. Elective arthroplasty should be postponed in patients who have active infections in the oral cavity until it has been cleared.

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QUESTION 4: Does the use of a urinary catheter during orthopaedic surgery increase the risk of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: The direct association between the use of a urinary catheter and a PJI remains controversial. However, as urinary tract infection (UTI) has been associated as a risk factor for PJIs in some studies, we recommend intermittent catheterization for postoperative urinary retention (POUR), or if an indwelling urinary catheter is utilized, removing it within 48 hours of insertion to minimize the risk of a UTI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 89%, Disagree: 6%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The role of routine urinary catheter use and the subsequent development of a PJI is unclear. However, urinary catheterization with indwelling catheters or intermittent catheterizations are associated with the development of UTIs [1–4]. A UTI is a one of the major causes of sepsis following total joint arthroplasty (TJA) [5]. The risk of UTI has been shown to be directly related to a duration of a urinary catheter for more than 48 hours [3,6]. This has been substantiated in the TJA literature [7,8].

The association between postoperative UTI and PJIs remains unclear. While several large scale studies have not found perioperative UTIs to be a risk factor for development of PJIs [9–11], in other studies postoperative UTIs have been associated with the subsequent development of PJIs [12–15]. This risk is theoretically due to bacteremia and hematogenous spread of pathogens into the prosthetic joint resulting in a PJI [16–20]; however, this has not necessarily been found in the literature [21–24].

To date, there is no study that has identified a direct association between urinary catheters and SSIs and PJIs. However, given the relationship with urinary catheterization and UTIs, and the association between UTIs and PJIs in some studies, bladder catheterization should be minimized. In recent studies of patients undergoing TJA without insertion of an indwelling catheter, POUR has been reported at rates as low as between 6.4 to 9.7% when using general anesthesia or opioid-free regional anesthesia [2,25,26]. This leaves greater than 90% of patients not exposed to catheterization. Furthermore, in a recent prospective randomized study, Huang et al. found a higher rate of UTI in patients who received an indwelling urinary catheter versus those who did not [2], which has been supported in another study [4]. While there are also studies that report no difference in the rates of UTI between patients who received indwelling catheters versus those who did not [27–29], if possible, patients undergoing TJA who are at a low risk for POUR, should not routinely have an indwelling urinary catheter placed and should be treated with intermittent bladder catheterization for POUR. If patients require an indwelling urinary catheter, it should be removed within 48 hours.

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QUESTION 5: Is routine urinary screening indicated prior to elective total joint arthroplasty (TJA)? If so, how should asymptomatic bacteriuria be treated prior to undergoing elective joint arthroplasty?

RECOMMENDATION: No. Routine urinary screening in asymptomatic patients is not recommended prior to elective TJA. There is also no evidence to demonstrate that preoperative treatment of asymptomatic bacteriuria is of any benefit.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 89%, Disagree: 9%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Concern with the genitourinary tract as a possible source of hematogenous seeding of bacteria into the joint has been present from as far back as the 1970s, when a few case reports [1–3] and a retrospective study [4] found a correlation between patients with periprosthetic joint infections (PJIs) and perioperative urinary tract infections (UTIs).

Presently, there seems to be extensive evidence supporting a definitive relation between perioperative symptomatic UTI and an increased risk of PJIs [5–16]. Consequently, it is widely accepted not only that treatment should be instituted, but also that surgery should be postponed in such a clinical scenario. Nevertheless, even this claim is not without dispute, as some reports do not corroborate this finding [17–20]. This data should not, however, be blindly extrapolated into conditions such as asymptomatic bacteriuria (ASB), as they are clearly two very different clinical scenarios.

Urinalysis is frequently used as a screening test to diagnose UTI in asymptomatic patients and a positive urine abnormality is often misinterpreted as definitive proof that the patient has a UTI [21]. A few studies focusing on screening asymptomatic patients with urinalysis were analyzed. All of them suggest that there is no relation between urine abnormalities and an increased risk of developing a PJI [22–25].

Urine cultures, regardless of urinalysis, are still the gold standard test for identifying UTIs in symptomatic patients and are perhaps the most reliable way to identify bacteriuria in asymptomatic patients. A systematic review of the literature was performed, confirming that ASB is a common finding in elective total joint arthroplasty candidates ranging from 5 to 19% [23,25–29]. This prevalence is also in agreement with previous descriptions of the prevalence of asymptomatic bacteriuria in similar age groups of the general population [30,31].

Results regarding a possible association between ASB and PJIs are scarce and conflicting (see Table 1). A large (around 2,500 patients) multicenter study by Sousa et al. [29] has found a statistically significant higher risk of PJI in ASB patients [29]. A similar more recent study, conducted within the UK National Health System and using the same definition for asymptomatic bacteriuria, found the

TABLE 1. Summary of asymptomatic bacteriuria and prosthetic joint infection rates major reports

Author, Year	Number of Joint Arthroplasties	Definition of Asymptomatic Bacteriuria	Patients without ASB		Patients with ASB		Follow-up	Major Finding(s)
			Number	Infection (%)	Number	Infection (%)		
Glynn 1984 [26]	299	Midstream urine specimens with significant bacterial growth (> 100,000)	242	0 (0.0)	57	2 (3.5)	3 months	- In all, 39 of 57 patients were operated on without antibiotic therapy; - Both surgical wound infections grew *Staphylococcus pyogenes* with previous *Escherichia coli* in urine isolate
Ritter 1987 [28]	364	Clean catch urine specimens with colony counts > 100,000	329	2 (0.6)	35	1 (2.9)	Up to 5 years	- All infected cases grew staphylococci including the patient that grew *Escherichia coli* in preoperative urine culture
Cordero-Ampuero 2013 [23]	471	> 100,000 colony-forming units *(only 181/471 patients with abnormal urinalysis proceeded with cultures)*	425	12 (2.8)	46	1 (2.2)		- 26 of the 46 ASB patients received specific antibiotic treatment for 7 days that began the operation day - in no case were the bacteria found in the joint the same as those in corresponding preoperative urine cultures
Sousa 2014 [29]	2, 497	Isolation ≥ 10^5 colony-forming units/mL in the absence of signs or symptoms of UTI	2,193	30 (1.4)	303	13 (4.3)	12 months	- PJI rate was significantly higher in the ASB group (OR: 3.23) although surgical isolates did not correlate to urine isolates; - Preoperative ASB treatment did not influence PJI rate – 3.9% (6/154) among treated vs. 4.7% (7/149) among untreated patients
Martínez-Vélez 2016 [25]	215	> 100,000 colony-forming units *(only 89/215 patients with abnormal urinalysis proceeded with cultures)*	204	0 (0.0)	11	1 (9.1)	>48 months	- Four of the 11 ASB patients received specific antibiotic treatment for 7 days that began the operation day - Infected case grew *Staphylococcus epidermidis* which differed from corresponding preoperative urine culture
Garcia-Nuño 2017 [33]	148	Isolation ≥ 10^5 colony-forming units/mL in the absence of signs or symptoms of UTI	121	2 (1.6)	27	2 (7.4)	N/R	- ASB was significantly more common in patients with dementia - There was one case in which the microorganism isolated intraoperatively coincided with the urine isolate *(P. aeruginosa)*
Honkanen 2018 [27]	20,226	All bacterial growth in the urine was considered significant	18, 848	133 (0.71)	1,378	7 (0.51)	12 months	- No statistically significant association was found between positive preoperative urine culture and PJI
Weale 2018 [39]	4,368	Isolation ≥ 10^5 colony-forming units/mL in the absence of signs or symptoms of UTI	4, 228	26 (0.61)	140	7 (5.0)	< 0.001	Up to 24 months
TOTAL	**28,588**		26,591	205 (0.8)	1,997	34 (1.7)	< 0.0001	

ASB, asymptomatic bacteriuria; UTI, urinary tract infection; OR, odds ratio

same statistical association [23]. Among the 5,542 patients included, 1,174 (21.2%) did not have a preoperative urine culture taken. A total of 4,368 (78.8%) had a preoperative urine culture taken within a year before the date of surgery, of which 140 (3.2%) had preoperative ASB. The infection rate in the ASB group was 5% (7/140), which was significantly higher than the 0.61% (26/4228) in the non-ASB group and the 1.96% (23/1174) in the group without a screening urine sample ($p < 0.001$). Although the difference was not statistically significant, they also found that the ASB group had a higher proportion of PJIs due to gram-negative bacteria despite all patients receiving preoperative treatment. Nevertheless, the ASB isolate was the same microorganism as the PJI isolate in only one of the seven cases.

Ollivere et al. [32] also studied the impact of asymptomatic urinary tract colonization in elective orthopaedic surgery, although they focused on outcomes other than PJI specifically. They found that 38% (15/39) of patients with preoperative ASB showed some form of postoperative delayed wound healing or confirmed superficial wound infection compared to 16% (83/511) of patients in the other subgroup, leading to a significantly increased relative risk of wound complications [32]. On the other hand, a recent study by Honkanen et al. [27] with over 20,000 patients [27] and several other smaller series [23,25,26,28,33] did not find an increased risk. One possible explanation for this potential statistical association is that ASB is not a risk factor in itself, but rather a marker for some kind of increased susceptibility [29,34].

What seems to be clear in interpreting all of the results of this systematic review is the lack of a clear causal relation. The overwhelming majority of PJI isolates are distinct from those previously found in the urine of asymptomatic total joint arthroplasty candidates [23,25–29,33]. This finding helps to understand the other clear result that ASB antibiotic therapy does not influence postoperative PJI risk [23,25–29,33]. Treating ASB not only seems not to influence PJI risk, but it also does not seem to prevent symptomatic UTI [22,35] from occurring after surgery (which might be a secondary benefit).

Following the current trend to recommend against treatment of asymptomatic bacteriuria except in cases of proven benefit, [36] the authors of this review believe that there is no place for urinary screening and treatment of asymptomatic bacteriuria before total joint arthroplasty. In addition, urinary abnormalities in asymptomatic patients should not be regarded as an indication to delay surgery. In fact, recent evidence seems to corroborate the lack of clinical utility of routinely screening urine in asymptomatic patients prior to elective total joint arthroplasty. Bailin et al. [37] performed a before-and-after study to analyze the impact of a new protocol for managing asymptomatic urinalysis abnormalities that aimed to reduce antibiotic prescriptions. After the new protocol was implemented, there was a significant decrease in antimicrobial prescriptions based on urine abnormalities both preoperatively and postoperatively. Notwithstanding, PJI rates after total joint arthroplasty neither increased in the immediate post intervention period nor in the ensuing years [37]. Lamb et al. [38] implemented an institutional policy to no longer routinely process urine specimens submitted from orthopaedic preoperative clinics. They performed a time-series analysis to evaluate the impact of this change on the incidence of PJIs. In the study period before policy change, 3,069 patients were screened of whom 352 (11.5%) had positive urine cultures and 43 of 352 (12.2%) received perioperative antibiotic treatment. Following the intervention, there were no further perioperative antibiotic courses for preoperative ASB. The periprosthetic joint infection rate was 0.03% (1 of 3,523) during the baseline period and did not change significantly during the intervention period 0.2% (3 of 1,891). None of the PJIs during the intervention period were caused by urinary pathogens [38]. Nevertheless, it is recommended that if a patient has irritating symptoms, screening tests such as urine dip sticks, white blood cell counts, and urine cultures should be considered.

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QUESTION 6: How should a patient with a symptomatic preoperative urinary tract infection (UTI) be managed prior to undergoing elective joint arthroplasty?

RECOMMENDATION: Preoperative symptomatic UTIs should be treated/eradicated with appropriate antibiotics prior to elective total joint arthroplasty (TJA).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 97%, Disagree:2%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

The potential link between asymptomatic bacteriuria, asymptomatic UTI, and symptomatic UTI with surgical site infection/periprosthetic joint infection (SSI/PJI) is an area of controversy in the arthroplasty literature. Given the low incidence of SSI/PJIs and the relatively low incidence of preoperative symptomatic UTI, the evidence for optimal management is limited. However, in light of the dire consequences of SSI/PJIs, every effort should be made to eliminate the sources and nidus of any infection, including UTIs, prior to elective orthopaedic procedures.

Perioperative symptomatic UTI has been shown to be a risk factor for SSI/PJI [1–3]. Pulido et al. [1] reviewed a prospective database of 9,245 primary TJA patients and found that postoperative UTI was a predisposing factor for PJIs (odds ratio (OR): 5.45, p = 0.04). The authors advocated for treatment and eradication of preoperative UTIs before proceeding with TJA [1]. Yassa et al. [2] reviewed 460 femoral neck fracture patients, 192 of which underwent hip arthroplasty. Ninety-nine patients (21.5%) had a preoperative UTI with 13 being chronic. All patients with UTI began treatment immediately with trimethoprim. Postoperatively, 57 of 460 patients (12.4%) had SSI, with a significantly higher proportion of those having had a preoperative UTI (rate ratio (RR): 2.47). The authors concluded that UTIs have a high prevalence in patients with femoral neck fractures and that it is an important risk factor for SSI [2]. Pokrzywa et al. [3] reviewed the American College of Surgeons (ACS) National Surgical Quality Improvement Program ((NSQIP) database of 434,802 general surgery patients and found that the preoperative UTI group had a higher incidence of infectious complications (OR: 1.515; 95% confidence interval (CI) 1.000 to 2.296) and non-infectious complications (OR: 1.683, 95% CI 1.012 to 2.799). The authors recommended treating UTIs prior to surgery and delaying elective procedures until resolution of the preoperative UTI [3].

The evidence available seems to indicate equivalent SSI/PJI rates between patients with appropriately-treated preoperative UTI and patients without UTI, though these studies are underpowered. Garg et al. [4] reviewed 150 primary TJA patients and found that those treated for preoperative UTIs had similar outcomes to patents without UTIs. Koulouvaris et al. [5] retrospectively reviewed 19,735 TJA patient records with 58 postoperative wound infections and matched those patients to 58 control patients. Of the 58 with SSI/PJIs, 3 had a preoperative UTI and 4 had a postoperative UTI, though only 1 SSI/PJI was the same organism as the urinary culture. In the matched control group, eight had a preoperative UTI and one had a postoperative UTI. The authors concluded that treated UTI (five to eight-day treatment course) had no greater likelihood of a postoperative infection than a patient without UTI. However, given the low infection rate of 0.29%, the power of the study was only 25%. Park et al. [6] reviewed 544 patients who underwent primary THA, 13 of which had a symptomatic UTI. The UTI patients were treated starting the day of surgery. Surgery was delayed in cases of fever or leukocytosis. There were no instances of SSI/PJI in either the case or control group,

and with only 13 patients with UTIs, with the study being underpowered [6].

To our knowledge, there are no studies reporting on symptomatic preoperative UTIs that are untreated prior to elective TJA. In light of the limited evidence, the best practice in management of symptomatic preoperative UTIs prior to elective TJAs is to treat and eradicate the infection before proceeding to surgery.

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QUESTION 7: Does preoperative urinary tract infection (UTI) (symptomatic and asymptomatic) increase the risk for subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Symptomatic UTI must be treated with appropriate antibiotics before proceeding with the surgery. In asymptomatic bacteriuria (ASB), treatment should be discontinued as it does not increase the risk of a subsequent SSI/PJI.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 96%, Disagree: 2%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

Urinary tract infections (UTIs) can present as symptomatic with fever, pain, raised leucocytes and large amount of pus cells in the urine or as asymptomatic bacteremia without any symptoms but > 10^5 CFU/ml in urine culture (two consecutive samples with the same organism in women and one sample in men) [1]. A correlation between UTI and PJI was first described in several case reports in the 1970s. However, there is a lack of evidence to support that correlation.

Reportedly, the prevalence of preoperative UTI ranged from 5.1 to 36% in female patients undergoing arthroplasties [2–10]. Most of these studies reported that patients with or without a positive urine culture had comparable PJI rates following arthroplasties [2–7,9,10]. On the other hand, one study reported that UTIs by gram-negative bacteria are a risk factor for PJI. However, that report could be biased because the insertion of urinary catheters, which is an important risk factor for PJI, was not stratified and the microorganisms in the PJI wounds were not the same as the isolates from the urine cultures [8].

The incidence of PJI ranges from 0.3 to 1% [11,12]. Distant seeding accounts for 10 to 20% of PJIs, and UTIs are estimated to be responsible for 13% of PJIs due to distant seeding [13]. By calculation, UTI accounts for only 0.01 to 0.05% of total PJIs. The frequency of ABU varies widely according to age, sex and population characteristics. Assuming that the prevalence of ABU is 5%, approximately 200,000 PJI patients are required to determine the causality of UTI for PJI. Such a study is barely feasible.

Urine culture is the most common diagnostic tool for UTI. However, the diagnostic accuracy of a urine culture is reduced in cases of inadequate preparation, sampling error and contamination during the collection of urine. Moreover, there is an inconsistency in the cutoff for diagnostic bacterial counts (> 10^5 colony-forming units of a microorganism or > 10^3 colony-forming units of a microorganism) [4,5]. Due to heterogeneity of diagnostic tests and different diagnostic criteria of UTIs, it was difficult to collect the overall data, to compare the results across the studies and to draw a convincing conclusion.

Evidence for Preoperative UTI as a Potential Risk Factor

In 2003, the American Urology Association (AUA) and the American Academy of Orthopaedic Surgeons (AAOS) conducted a case control study of 47 cases and 200 controls and jointly identified urinary tract infections as an important risk factor for PJIs among other risk factors [14]. Luis et al. conducted a prospective review of 9,245 patients with joint arthroplasties and identified preoperative UTI as an important modifiable risk factor for PJIs and instituted preoperative screening and treatment for UTI before proceeding for surgery [11]. Yassa et al. conducted a retrospective cohort analysis of patients who underwent an emergency surgery within 24 hours for femoral neck fractures and examined the prevalence of urinary tract associated PJIs in these patients. Out of the 367 patients enrolled, 57 (12.4%) had a surgical site infection with 23 (40%) having a preoperative UTI. They concluded that a preoperative UTI is an important risk factor for PJI and requires treatment [15].

However, a study by Kuolovaris et al. reviewed medical records of 19,735 patients and did not find any relationship between preoperative UTIs and PJIs. Only one of their 58 patients had a PJI due to the same organism causing a UTI. However, this was an underpowered study ($\beta = 25\%$). Another study by Garg et al. showed that

preoperative UTIs, when adequately treated with appropriate antibiotics, have similar outcomes as non-UTI patients [16]. Thus, symptomatic preoperative UTIs must be treated before proceeding with surgery.

Evidence for Preoperative Asymptomatic Bacteriuria (ASB)

A cohort study conducted by Glynn et al. in 1984 showed that ASB predisposes to superficial wound infections, though the organisms were different from that of the urine culture [3]. In another retrospective cohort study, Ritter et al. enrolled 277 patients who underwent arthroplasty, and 35 cases of preoperative ASB were identified. During the follow-up period, varying from one to 16 years, they identified three cases of PJI, but none were related to the preoperative ASB [17]. Ollivere et al., in their prospective study of 600 patients, showed that 36% of their patients with ASB had some form of delayed wound infections vs. 16% in the non-ASB group. They concluded that patients with ASB should be recognized as a high-risk subgroup for wound infections postoperatively irrespective of their treatment [18].

A randomized controlled trial of 441 patients undergoing arthroplasty found 42 patients with asymptomatic bacteriuria. Patients were randomized to specific urinary treatment (Group A) and no specific treatment (Group B) if the urine culture was positive. Six patients each in group A and B had wound infections after three months of follow-up. None of the organisms were similar to that of the urine culture. Thus, no urinary origin of PJI was identified in patients with asymptomatic bacteriuria irrespective of whether treatment was given or not [2]. A multicentric cohort study conducted by Sousa et al. found an ASB prevalence of 12.1% among 2,497 patients. They observed that the PJI rate was significantly higher in the ASB group than in the non-ASB group (4.3 vs. 1.4%; odds ratio (OR) 3.23, 95% confidence interval (CI), 1.67 to 6.27, p = .001). However, in the ASB group, there was no significant difference in PJI rate between treated (3.9%) and untreated (4.7%) patients. They concluded that preoperative treatment of ASB did not show any benefit and could not be recommended [8]. Other studies by Martinez et al., Gou et al. and Bouvet et al. also suggest similar findings [5,19,20]. Systematic reviews and a meta-analysis conducted by the European Association of Urology, Mayne et al. and Zhang et al. also concluded that detection and treatment of ASB has no benefit for patients undergoing joint arthroplasty [21–23].

All of these studies have cautioned against the adverse effects of antibiotics such as drug resistance, economic burden and potential allergies. A study conducted with the help of a multidisciplinary team comprised of orthopaedic surgeons, hospitalists, preoperative clinic nurses, infection control professionals, infectious diseases physicians and microbiologists decided to change their policy regarding preoperative urine culture screening, and no screening cultures were to be sent before an elective primary joint arthroplasty (EJA). A total of 5,414 primary EJAs were enrolled over a three-year period. Of these, 3,523 were in the baseline period, and 1,893 were during the intervention period. They did not find a significant increase in PJI in the intervention phase. Also, discontinuation of urine screening led to cost savings by eliminating urine cultures and also the cost of antibiotics prescribed for ASB; thus, there is good evidence to stop screening and treatment of patients for asymptomatic bacteriuria as it does not increase the risk of PJIs [24].

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QUESTION 8: Does a patient with a colostomy have an increased risk for surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: There is currently no evidence in the literature to determine if a patient with a colostomy is at an increased risk for SSI/PJIs following an arthroplasty procedure. However, it is our recommendation to ensure that the patient has a leak-free and clean colostomy in place to prevent soiling.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

There are several risks factors associated with SSIs or PJIs such as body mass index (BMI), diabetes mellitus (DM), rheumatoid arthritis (RA), depression, chronic corticosteroid use, hypoalbuminemia and previous joint surgery [1–4]. Furthermore, other risk factors are reported to be correlated but not significantly associated with PJIs. These include cirrhosis, hypothyroidism, urinary tract infection, illicit drug and alcohol abuse, dementia, hypercholesterolemia, hypertension, ischemic heart disease, peptic ulcer disease as well as hemiplegia or paraplegia [4].

Colostomy is a surgical procedure diverting a part of the colon to an artificial opening in the anterior abdominal wall. It may be performed for emergency or elective surgical conditions for the management of a wide range of congenital and acquired conditions, as well as for benign or malignant gastrointestinal conditions for two main purposes: diversion or decompression of the colon [5,6]. Although it is a lifesaving procedure, both its construction and reversal have high morbidity and mortality [7,8]. Surgical site infection after colostomy is reported to be one of its major complications [5].

Correlation between bowel diseases and procedures and infection in the hip joint has been reported. Colon-articular fistulas involving the hip have been reported in patients with inflammatory bowel disease [9], diverticular disease [10] and bowel carcinoma [11]. In addition, solitary case reports have described fistula formation following total hip arthroplasty [12] or Girdlestone resection arthroplasty [13]. Coelho-Prabhu et al. [14], in a prospective, single-center, case-control study, demonstrated that esophagogastroduodenoscopy with biopsy was correlated with increased risk (odds ratio (OR) = 3, 95%, confidence interval (CI) 1.1 to 7) of PJI in arthroplasty patients.

There is no publication on the subject of colostomy and the potential risk for SSI/PJI following arthroplasty. The data available suggest that SSI around the abdomen are risk factors associated with colostomy. By way of speculation, we feel that a patient with a colostomy, who has developed a SSI, would be at risk for developing a PJI after elective arthroplasty. Thus, it is justified to propose that elective arthroplasty should be delayed in patients with an active infection around the colostomy. Furthermore, it must be ensured that patients have a clean, leak-free and properly functioning colostomy in place prior to elective arthroplasty. Consideration may be given to waiting until a temporary colostomy is reversed before proceeding with an elective arthroplasty.

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1.2. PREVENTION: HOST RELATED, GENERAL FACTORS

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QUESTION 1: What modifiable and non-modifiable host factors contribute to an increased risk of surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Modifiable host factors such as body mass index (BMI), smoking and alcohol, as well as certain medical co-morbidities have been shown to increase the risk of SSIs/PJIs. Non-modifiable factors such as increasing age, male gender and black ethnicity have also been shown to increase the risk of SSIs/PJIs.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

The risk of developing SSIs/PJIs following total joint arthroplasty (TJA) is likely to be influenced by several factors such as the characteristics of the patients, the surgical intervention and the postoperative care (Table 1). However, patient- or host-related factors such as socio-demographic characteristics, body mass index and medical and surgical histories seem to play an important role in the development of SSIs/PJIs. With the exception of factors such as age and sex, many patient factors are modifiable and could potentially be used for the identification of patients at high risk of developing SSIs/PJIs as well as targeting appropriate interventions. The literature has a plethora of studies that have evaluated the associations of these potential host factors and the risk of SSIs/PJIs. However, some of the findings have been inconclusive because of inconsistent results reported. We sought to clarify the evidence by conducting a comprehensive systematic review of the literature.

There is inconsistent evidence on whether age contributes to an increased risk of PJI. The meta-analysis by Chen et al. showed no association between age and risk of infection [1]. In a pooled analysis of eight studies, age (as a continuous exposure) was not associated with the risk of PJI [2]. However, findings from two studies suggested that patients aged 75 years and above had an increased risk of SSI following primary total hip arthroplasty (THA) [3,4].

The effect of gender on the risk of PJI has inconsistently results. While some studies suggest males are at an increased risk of developing PJI following joint arthroplasty, others suggest differently. However, the emerging evidence is more in favor of males being more likely to develop infection compared to females. In a pooled analysis of eight studies, Chen et al. demonstrated that males had a higher risk of infection after total knee arthroplasty (TKA) than females [1]. A recent pooled multivariate analysis of 28 studies confirms this emerging evidence of higher risk in males [2].

Pooled analyses have shown that black populations (compared with white race) have an increased risk of PJI/SSI [5–11]. However, the evidence for Hispanic ethnicity, native Americans, Eskimos and Asian populations is inconsistent and not significant [5–11].

One study reported a decreased risk of PJIs, and another reported an increased risk, comparing patients in rural locations versus non-rural locations [12,13]. Compared with THAs, TKAs were consistently associated with an increased risk of PJI/SSI [14–16].

The evidence for the association between BMI and increased risk of SSI/PJI is consistent. In a pooled analysis of 14 studies, Kerkhoffs et al. reported an increased risk of infection following TKA when obese were compared to non-obese patients [17]. Yuan et al. also reported a two-fold increase risk of surgical site infections for obesity [18]. In a pooled analysis of 29 studies included in the most recent review, high BMI (overweight and obesity) was associated with an increased risk of SSI/PJI [2]. The association was consistent with a dose-response relationship. One study compared underweight (BMI < 18.5 kg/m^2) versus a normal to overweight BMI category but found no association with PJI [19].

The evidence on the association between a history of hypertension and risk of PJI/SSI is inconsistent. A pooled analysis of six studies showed no significant evidence of an association [6,20–24].

A pooled analysis of six studies showed high alcohol consumption or alcohol abuse was associated with a higher risk of PJI/SSI following TJA [5,6,20,23,25,26].

Consistent evidence shows that a low income is associated with an increased risk of PJI/SSI [7,11,27]. Malnutrition (as measured by low serum albumin) was demonstrated to be associated with an increased risk of PJI/SSI in a pooled analysis of five studies [28–32].

An increasing amount of literature has shown that smoking has a negative effect on postoperative outcomes. However, the evidence has been mostly inconsistent regarding the association between smoking and risk of PJI following TJA. However, in a recent pooled analysis of eight studies, smokers were shown to have an increased risk of PJI compared to non-smokers [2]. Robust evidence suggests that smoking cessation before surgery is associated with more than a 50% decrease in the risk of postoperative infection [33].

Consistent evidence suggests that in patients undergoing surgery, diabetes mellitus (DM) is associated with an increased risk for complications. In a pooled analysis of 10 retrospective studies, Tsang and Gaston found DM to be associated with a two-fold increased risk of established SSI after elective THA [34]. Yang et al. in a pooled analysis of eight studies demonstrated the prevalence of DM to be associated with an increased risk of deep infection after elective primary TKA [35]. In another pooled analysis of eight studies, Zhu et al. showed DM to be associated with an increased risk of PJI following TJA [36]. In the most recently pooled analysis of 29 studies, DM was associated with an increased risk of PJI [2].

A pooled analysis of seven studies reported inconsistent findings with respect to the association between a history of cardiovascular disease and PJI/SSI risk after TJA [20,23,37–42]. In a pooled analysis of studies that evaluated congestive heart failure (CHF) and cardiac arrhythmias as risk factors, significant associations were demonstrated [5,6,20,23,43]. A history of peripheral vascular disease was associated with an increased risk of PJI/SSI in a pooled analysis of six studies [5,6,20,23,43,44].

TABLE 1. Summary of risk factors associated with development of SSI/PJI

Modifiable Host Factors	Factors with Limited Evidence of Associations with SSI/PJI
• BMI – Strong • Smoking – Strong • High alcohol intake (alcohol abuse) – Strong • Low income - Strong • Malnutrition (low serum albumin) – Strong • History of DM – Strong • History of CVD – Moderate • History of CHF – Strong • History of cardiac arrhythmia – Strong • History of PVD – Strong • Chronic pulmonary disease – Strong • Chronic obstructive pulmonary disease – Strong • History of renal disease – Strong • History of liver disease/cirrhosis – Strong • History of RA – Strong • History of cancer/malignancy – Strong • History of osteonecrosis – Strong • History of depression – Strong • History of psychosis – Strong • History of HIV/AIDS – Strong • Neurologic disease (hemiplegia, paraplegia) – Moderate • History of corticosteroid administration – Strong • History of intra-articular corticosteroid injection – Moderate • Previous joint surgery – Strong • Revision arthroplasty – Strong • Previous joint infection – Moderate • Frailty – Moderate • Preoperative anemia – Strong • ASA grade > 2 – Strong • Charlson comorbidity index (high) – Strong • Preoperative hyperglycemia and high HbA1c – Moderate • Allogenic blood transfusion – Strong • Prophylaxis with warfarin or low molecular weight heparin – Moderate	• Age (as a continuous exposure) – Limited • Hispanic ethnicity – Limited • Native American and Eskimo ethnicity – Limited • Asian race – Limited • History of drug abuse – Limited • Rural location vs. non-rural location – Limited • Underweight – Limited • History of hypertension – Limited • History of osteoarthritis – Limited • History of post-traumatic arthritis – Limited • Low- or high-risk dental procedures – Limited • History of UTI – Limited • History of dementia – Limited • Hypercholesterolemia – Limited • Peptic ulcer disease – Limited • Valvular disease – Limited • Metastatic tumor – Limited • History of coagulopathy – Limited • History of venous thromboembolism – Limited • Pulmonary circulatory disorders – Limited • Hypothyroidism – Limited • Hepatitis (B or C) – Limited • Electrolyte imbalance – Limited • Autogenous blood transfusion – Limited
Non-modifiable Host Factors	
• Age (≥ 75 years) – Moderate • Male sex – Strong • Black race – Strong • TKA vs. THA – Strong	

ASA, American Society of Anaesthesiologists physical status score; DM, diabetes mellitus; CVD, Cerebro vascular disease; CHF, congestive heart failure; PVD, peripheral vascular disease; RA, rheumatoid arthritis; TKA, total knee arthroplasty; THA, total hip arthroplasty; SSI, surgical site infection; PJI, periprosthetic joint infection; UTI, uninary tract infection

A pooled analysis of four studies evaluating the associations of chronic pulmonary disease with risk of PJI, showed no significant evidence of an association [5,20,23,43]. However, three of the studies reported consistent significant associations. Chronic obstructive pulmonary disease was associated with an increased risk of PJI/SSI in a pooled analysis of four studies [9,16,22,45].

In a pooled analysis of eight studies, renal disease was significantly associated with an increased risk of PJI/SSI [5,6,20,23,43,46–48]. A history of liver disease or cirrhosis of the liver was associated with an increased risk of PJI/SSI [5,6,20,23,43,44,48]. However, a history of hepatitis B or C infection was not associated with increased risk of PJI/SSI [16,44,48].

A pooled analysis of seven studies showed rheumatoid arthritis (RA) to be associated with an increased risk of PJI following TKA [1]. In another pooled analysis of seven studies, Zhu et al. demonstrated RA to be associated with an increased risk of PJI [36]. Findings of a recent pooled analysis of 13 studies confirms the accumulating evidence [2].

A history of cancer or malignancy was associated with an increased risk of PJI/SSI following arthroplasty in a pooled analysis of seven studies [5,6,16,20,23,28,49] However, evidence on the association between metastatic tumors and risk of PJI/SSI was limited and inconsistent [6,20,23,43].

A history of coagulopathy was not associated with PJI/SSI in a pooled analysis of four studies with inconsistent findings [5,6,20,23]. A single study reported evidence of an association between venous thromboembolism and PJI, but this was based on univariate analysis [15].

A pooled analysis of three studies showed a history of osteonecrosis to be associated with an increased risk of PJI/SSI [10,19,50].

Evidence suggested that histories of depression and psychosis were each associated with an increased risk of PJI following total joint arthroplasty [6,20,23].

A pooled analysis showed a history of HIV/AIDS infection to be associated with an increased risk of PJI/SSI [6,43,44,51].

A history of neurologic disease such as hemiplegia/paraplegia was associated with an increased risk of PJI/SSI in a pooled analysis of four studies with inconsistent findings [5,20,23].

A previous meta-analysis of four studies suggested a history of corticosteroid therapy to be associated with an increased risk of PJI following TKA [1]. Zhu et al. also demonstrated corticosteroid therapy to be associated with an increased risk of PJI following total joint arthroplasty in a pooled analysis of five studies [36]. In the most recent pooled analysis of 10 studies, the findings were consistent with previous evidence [2]. The literature has been inconsistent and weak on whether intra-articular corticosteroid injections administered for osteoarthritis increases the risk of infection following joint arthroplasty. In a previous systematic of nine studies, Pereira et al. found no significant evidence to indicate the presence of an association. In a recent meta-analysis, use of intra-articular corticosteroid injection was not statistically significantly associated with an increased risk of PJI [2]. However, an update of recent evidence which involved pooling of five studies with usable data demonstrated a significant association. Quality of the evidence was moderate.

In a pooled analysis of five studies, a history of previous joint surgery (vs. no previous joint surgery) was associated with about a three-fold increased risk of PJI [2]. When compared with primary arthroplasty, revision arthroplasty was associated with an increased risk of PJI in a pooled analysis of five studies [2]. Two studies reported a history of previous joint infection to be associated with an increased risk of PJI, but the findings were based on univariate analysis [45,52].

A single high-quality study reported an increased risk of PJI comparing frail patients with non-frail patients [12].

Consistent evidence showed that preoperative anemia was associated with an increased risk of PJI/SSI following TJA [20,23,43,53].

An American Society of Anesthesiologists (*ASA*) grade of > 2 was associated with an increased risk of PJI/SSI, and this was consistent across all studies [3,9,10,15,19,54].

Though the exposures were not comparable and therefore could not be pooled, there was consistent evidence showing that a higher Charlson comorbidity index was associated with an increased risk of PJI/SSI [7,8,11].

Pooled evidence from seven studies showed no significant association of osteoarthritis with the risk of PJI following joint arthroplasty [10,19,25,50,55–57].

A pooled analysis of three studies showed no evidence of an association between post-traumatic arthritis and risk of PJI/SSI [10,19,57].

In two studies that evaluated the association of dental procedures with risk of PJI, there was no evidence of any significant associations of PJI with dental procedures [13,58].

There was no evidence of an association between uninary tract infection (UTI) and the risk of PJI/SSI in all studies examined [20,23,38]. This was the same for dementia and PJI/SSI [16,20,23].

None of the studies which evaluated the associations of hypercholesterolemia as well as peptic ulcer disease with the risk of PJI, showed any evidence of associations [6,20,23].

Evidence on the association between valvular disease and risk of PJI/SSI was limited and inconsistent [5,6,20,23]. In a pooled analysis, there was no significant evidence of associations of PJI/SSI with a history of pulmonary circulatory disorders, [5,20,23,43] history of hypothyroidism [6,20,23,59] and a history of drug abuse [6,20,23].

There was no significant evidence of an association between electrolyte imbalance and risk of PJI/SSI [6,60]. The evidence on the association of preoperative hyperglycemia and high HbA1c levels with risk of PJI/SSI was mostly inconsistent and could not be pooled because the exposures were not comparable [14,61–64], but the evidence suggests that these factors might be associated with an increased risk.

Patients who receive allogeneic blood transfusions are at increased risk of SSI/PJI [15,43,65–67]; however, the evidence is limited for autogenous blood transfusions [43]. Prophylaxis with warfarin or low molecular weight heparin for venous thromboembolism was associated with an increased risk of PJI [68,69].

SEARCH STRATEGY

Data sources. Medline, Embase, Web of Science, Cochrane Library and reference lists of relevant studies from inception to February 15, 2018.

Selection criteria. To be included, studies were to be longitudinal studies (observational studies and randomized controlled trials (RCTs)) that have evaluated the associations of patient-related factors and the risk of surgical site infections (SSIs) and/or periprosthetic joint infections (PJIs) in patients undergoing orthopaedic procedures.

Review methods. The relative risk (RR) with 95% confidence intervals was used as the summary measure of association across studies. Study-specific RRs with 95% confidence intervals were meta-analyzed using random effect models.

Results. Of 7,177 potentially relevant citations, 101 studies were finally included in this review. No RCTs relevant to the review topic were identified.

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QUESTION 2: Are there any genetic factors that predispose patients to surgical site infection/periprosthetic joint infection (SSI/PJI) or predict the success of the treatment for SSI/PJI?

RECOMMENDATION: The evidence suggests a potential heritable predisposition is possible, but there is a lack of definitive evidence supporting specific genetic risk factors for SSI/PJI after total joint arthroplasty (TJA).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

It is hypothesized that individuals may be susceptible to SSIs and PJIs owing to patient-related genetic characteristics. This situation may result from polymorphisms in genes encoding various proteins, receptor intracellular signaling mediators, cytokines, and enzymes vital to the functionality of the host's immune system.

In hopes of allowing for early targeted prevention in high-risk patients, risk calculators have been developed to identify patients at greater risk for developing infection following TJA. However, it has been suggested that these scoring systems are limited in their ability to accurately identify individuals at high risk and very few of them have been externally validated [1,2]. Kunutsor et al. reported that none of the risk scores they reviewed underwent subsequent impact studies to determine their utility for clinical decision-making [2]. Thus, other methods of early identification are needed in order to influence clinical decisions.

Genetic susceptibility testing has broadening interest as a means to identify patients at high risk for infection [3], specifically PJIs [4]. However, such a test has yet to be developed and implemented in the arthroplasty arena. When evaluating the immune response to mycobacterial infections, Blischak et al. reported that the innate immune system may play a role in bacterial infections [5]. Evaluating patients with multiple TJAs, Bedair et al. suggested that some patients may be at greater risk for infection due to subclinical immune deficiencies [6]. In 2013, a large population-based study by Lee et al. reported familial susceptibility to SSI which included, but was not limited to, PJI [7]. Similarly, Anderson et al. demonstrated familial clustering in TJA patients who suffered a PJI [8]. They were able to show an increased risk of PJI following TJA in relatives of patients who have experienced a PJI [8]. These families demonstrated infection rates of 9 to 17% compared to rates of approximately 2.3% in relatives of patients without PJI. Given the current literature, a heritable risk for PJI seems reasonable.

Regarding specific genetic factors, recent reports suggest that genetic variants associated with mannose-binding lectin (MBL) may be associated with an increased risk of infection in general [9,10] and in PJI populations specifically [11,12]. Burgner et al. also reported on several candidate genes identified in the literature that may be related to innate immunity [3]. For example, they noted the association of toll-like receptor (TLR) genes, *TLR2* and *TLR4* and bacterial infections [3]. Sutherland et al. performed a genetic association study on patients admitted to an intensive care unit who had evidence of infection [13]. Ultimately, they reported that the CD14, *MBL* and *TLR2*

polymorphisms were associated with a greater prevalence of infection in critically ill adults. However, others report no association between the CD14 polymorphism and the incidence of infection [14]. Agnese et al. were, however, able to associate the *TLR4* mutation with an increased incidence of bacterial infections [14]. Aside from the *MBL* mutations, the CD14, *TLR2*, and *TLR4* have been reported as not being associated with infections in the PJI literature [15]. Furthermore, a recent systematic review on the genetic susceptibility to PJI concluded that although evidence exists supporting a genetic role in PJI, no definitive conclusions can be made given the relatively small amount of data available in the existing literature [15].

In summary, despite the evidence suggesting a heritable risk for infection, there is a scarcity of robust studies providing evidence on genetic risk factors for infection. Additional evidence is needed, perhaps targeting *MBL* variants, in order to consider genetic risk factors and to identify patients at greater risk for infection. Such studies may contribute to our understanding of the pathogenesis of SSI/PJI.

Given the evidence suggesting a genetic susceptibility to SSI/PJI, it seems reasonable that genetic factors may also play a role in the treatment outcomes for infection. Early studies on the ability to predict treatment outcomes of bacterial and fungal infections were not encouraging and relied on antimicrobial susceptibility tests [16–20]. Clinical and genetic risk factors for predicting treatment response has been reported for a variety of diseases [3,21–23]. Furthermore, recent studies evaluating the treatment response in patients with hepatitis and human immunodeficiency viral infections suggest that pre-treatment genetic markers exist which could increase the understanding of the patient's treatment response to anti-viral therapies [24–28]. However, there is little, if any, evidence on the ability of host genetic factors to predict treatment outcomes for surgical site or periprosthetic joint infections.

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QUESTION 3: Does current tobacco use increase the risk of surgical site infection/periprosthetic joint infection (SSI/PJI) recurrence?

RECOMMENDATION: Yes. Current tobacco use appears to increase the risk of SSI/PJI in patients undergoing orthopaedic procedures.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 94%, Disagree: 3%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

PJI is a devastating potential complication after total joint arthroplasty (TJA) procedures. Studies have shown that this complication occurs approximately 1 to 2% of the time following primary TJA, and is even more common following revision surgery [1–3]. Surgical treatments of PJI, with the goal of infection eradication, include irrigation and debridement with implant retention, one-stage revision and two-stage revision procedures. There are no standard definitions for successful treatment but most physicians would agree that the goal of these interventions is to eradicate the infection. Reported success rates of the aforementioned procedures vary and there exists abundant literature focusing on the impact of various patient, surgical and infectious factors on treatment success. Despite the large number of studies on factors contributing to the recurrence of PJI following surgical treatment, relatively little has been published looking at the impact of current tobacco use on PJI recurrence.

An extensive systematic review was performed to identify all studies reporting the success of surgical treatments for hip or knee PJI. This literature review identified 20 published studies that specifically reported or evaluated tobacco use in the study population or in relation to the surgical treatment of SSI/PJI [4–23]. Using the methodology for evaluating evidence as outlined by the American Academy of Orthopaedic Surgeons Clinical Practice Guideline and Systematic Review Methodology Version 2.0 [24], 17 of these studies were graded as being low-quality [4,5,7,8,10–12,14–23], and three studies were graded as being very low-quality [6,9,13].

Of the 20 studies evaluated, 14 studies evaluated two-stage revisions; two studies evaluated irrigation and debridement, and five studies evaluated patients with either of those two procedures for PJI. Univariate statistical analysis evaluating the association between tobacco use and recurrence of PJI was performed in 19 of the studies. Smoking was associated with a significantly increased risk for PJI recurrence in three of these studies [4,8,9]. Further multivariate analysis was performed in two of these studies [4,9]. Hoell et al. retrospectively evaluated 59 patients who underwent two-stage revision for PJI and identified smoking as an independent risk factor for failure to cure infection (odds ratio (OR): 21.5, 95% confidence interval (CI) 2.6 to 178) [9]. Cancienne et al. utilized the Medicare administrative claims dataset to evaluate 18,533 patients who underwent antibiotic spacer placement for infected total knee arthroplasty and found tobacco use to be independently associated with the need for a repeat debridement without reimplantation within one year (OR 1.10, $p = 0.003$) [4].

Given that many of the studies had relatively small cohorts and may have been underpowered to detect an association between smoking and PJI recurrence, pooled analysis on the studies was performed. Of the 20 studies, 12 provided sufficient data to be included in the pooled analysis [5,6,8,10–14,18–21]. The remainder either did not report raw data on the number of patients who used tobacco or did not report on how many tobacco users had a recurrence of PJI. If there were multiple studies from the same institution, only the most recent study with the largest cohort was included. This was done to prevent the unintentional inclusion of the same patient data multiple times. This left ten studies, representing 1,124 patients with PJI, to be included in the pooled analysis [5,6,8,10,12–14,19–21]. Heterogeneity across studies was present as determined using the Q and I^2 statistics or likelihood ratio test. Therefore, inverse-variance weighted random-effects models were used to evaluate the pooled estimates using R software. Forest plots were also generated to display the odds ratios and 95% confidence intervals for each study, as well as the overall random-effects pooled estimate and its confidence interval. Pooled analysis demonstrated that tobacco users were significantly more likely to experience recurrence of PJI after surgical treatment than non-tobacco users, with an OR of 1.53 (1.06 to 2.21) (see Fig. 1). Furthermore, this finding remained significant when only including patients treated with two-stage revision (OR: 1.59, 1.03 to 2.47).

The findings from these studies and the results of the pooled analysis suggest that current tobacco use increases the risk of PJI recurrence after surgical treatment of hip and knee PJI. The strength of this conclusion is limited by the available studies being of low or very low quality and primarily including small numbers of patients. However, there is higher quality literature that associates current tobacco use with an increased risk of PJI following primary TJA [25–30]. There are also established adverse effects of tobacco use on wound healing. It is therefore reasonable to conclude that the findings from these studies and the results of the pooled analyses likely represent a true association. There is a need for additional, high-quality research to confirm this association and to assess whether cessation of tobacco use can increase the success of infection remission following surgical treatment for PJI.

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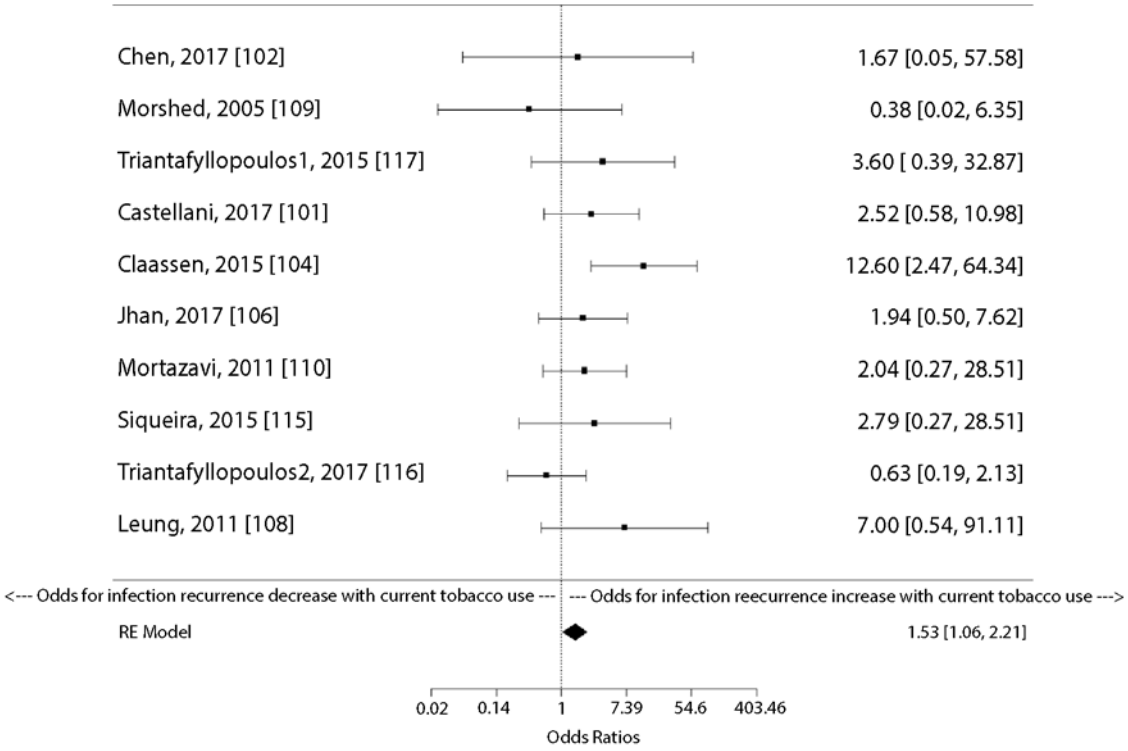

FIGURE 1. Odds ratios for infection recurrence with current tobacco use versus no tobacco use.

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QUESTION 4: Do underweight patients (body mass index (BMI) < 18.5Kg/m2) have a higher risk of surgical site infection/periprosthetic joint infection (SSI/PJI) following orthopaedic procedures? If yes, does increasing the BMI in underweight patients reduce the risk of SSI/PJI?

RECOMMENDATION: Yes. Underweight patients (BMI < 18.5K/m2) have a higher risk of SSI/PJI following orthopaedic procedures. However, there is no current evidence indicating that an increase in the BMI of an underweight individual has an effect on reducing the risk of SSI/PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 4%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

BMI abnormalities have been associated with worse outcomes in surgical patients. Most studies have focused on comparisons between obese patients and those of normal weight (NW) in finding that higher BMI is associated with a higher incidence of infections [1–6]. Underweight (UW) patients are typically defined as having a BMI of less than 18.5 kg/m^2 [7]. UW patients make up 2.3% of the United States population and up to 3.66% of patients in European nations [8,9]. In the field of general surgery, UW patients have been shown to have higher complication rates compared to overweight and obese patients [7,10–12]. Similarly, UW total joint arthroplasty (TJA) patients have also been identified as having a higher incidence of infection, transfusion, dislocation, readmission and mortality [1,3,13,14]. No studies have been identified that evaluate the risk reduction when increasing the BMI in these patients.

Saucedo et al. [1] evaluated readmission risk in cohorts of both total knee arthroplasty (TKA) and total hip arthroplasty (THA) patients. Compared to NW patients (defined as BMI 18.5 to 24.9 kg/m^2 in this study), UW status was a significant risk factor for readmission at 30 and 90 days postoperatively (16.4 and 11.6%, respectively) with postoperative infection being the leading cause for readmission [1]. A separate study evaluating infection risk factors in patients with rheumatoid arthritis showed that UW status also had an increased risk of infection, (odds ratio (OR) 6.0, 95% confidence interval (CI) 1.2 to 30.9, p = 0.033) [13]. Also, a study by Nafiu et al. demonstrated worse TJA outcomes and higher SSI rates in UW minorities [11]. When patients were stratified based on BMI, the study found SSI rates of 3% in the UW group, 1.3% in the NW group, 1.4% in the overweight group, 1.5% in the obese group and 1.7% in severely obese patients, respectively (p < 0.001) [11].

When specifically evaluating TKA, similar results have been found. Manrique et al. compared UW TKA patients to a cohort of NW TKA patients and found that UW individuals had a higher rate of SSI (11.1%) than did NW individuals (0%) (p = 0.01) [15]. UW patients also had an increased risk of SSI (OR: 23.3; 95% CI 1.2 to 466, p = 0.04) compared to NW patients. This study and others utilized the SSI definition specified by the Centers for Disease Control (CDC) criteria [16]. The CDC SSI criteria was used instead of the Musculoskeletal Infection Society (MSIS) and International Consensus Meeting (ICM) definitions for periprosthetic joint infection (PJI) [17] because the MSIS and ICM criteria were not available at the time of publication.

While there is evidence that UW status increases risk of SSI/PJI, there are a few database studies that contradict these findings. Using the New Zealand joint registry, Murgatroyd et al. showed no increased risk of deep infection at a maximum of two-year follow-up [18]. Of the 5,357 patients, 131 were UW (2.4%). However, UW was defined as BMI < 20 kg/m^2 in this study [18]. All seven reported deep infections occurred in the overweight and obese groups with zero in the UW group at two years [18]. SSI and wound infections were not reported.

Another registry study, utilizing the Clinical Practice Research Datalink of 31,817 patients, found six-month wound infection rates of 1.5% (BMI < 18.5 kg/m^2), 2.2% (BMI = 18.5 to 25 kg/m^2), 3.0% (BMI = 25 to 30 kg/m^2), 3.3% (BMI = 30 to 35 kg/m^2) and 3.1% (BMI > 35 kg/m^2) respectively, with UW patients having the lowest wound infection rate [19]. Deep infection rates were not reported. In addition, discharge data from the National Inpatient Sample found that UW individuals (BMI < 18.5 kg/m^2 in this study) had a decreased rate of postoperative infection (OR 0.23, 95% CI 0.09 to 0.61) [20]. Importantly, all three of these studies possessed the limitations inherent to the analysis of large administrative databases (i.e., errors in data collection, incomplete data sets and observer bias) particularly with the diagnoses of postoperative infection, SSI and PJI.

Overall, there is an established association between low BMI and poorer surgical outcomes, specifically infection, in a variety of disciplines, including TJA in orthopaedics [10–12,19–26]. Furthermore, higher transfusion rates were also observed among UW patients after surgical intervention [11,13,15]. Postoperative allogeneic transfusion has been demonstrated to be an independent risk factor for developing SSI and PJI [27]. A lower BMI may be an indirect measure of nutritional status, as lower BMI patients have been shown to have lower levels of albumin, prealbumin, and protein- all of which can be used to evaluate nutritional status [28]. Low BMI patients have decreased reserves and an inability to accurately react to stress secondary to their suppressed immune systems [29]. Low BMI has also been associated with higher morbidity and mortality

rates possibly reflecting an altered physiological state [30]. A potential optimization of this status resulting in a BMI increase in UW patients could be beneficial by decreasing their risk of adverse events. Increasing BMI to mitigate SSI and PJI risk in UW individuals is an area for future study.

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QUESTION 5: (A) What upper body mass index (BMI) threshold is associated with an increased risk of surgical site infection/periprosthetic joint infection (SSI/PJI)? (B) Does implementation of these cutoffs reduce the incidence of SSI/PJI?

RECOMMENDATION:

A) Obesity increases the risk of SSI/PJI after total joint arthroplasty (TJA). The risk increases gradually throughout the full range of BMI rather than surging at a certain cutoff point. A substantially increased risk is noticed in patients with a BMI > 40 Kg/m^2 and the risks of surgery must be carefully weighed against its benefits in these patients.

B) Weight reduction prior to surgery may have a benefit in mitigating risk for SSI/PJI for all patients with a BMI above normal.

LEVEL OF EVIDENCE: A) Strong, B) Consensus

DELEGATE VOTE: Agree: 95%, Disagree: 2%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

Obesity has been shown to play a negative role throughout the natural history of osteoarthritis, from the development and progression of the disease to the occurrence of postoperative complications [1–5]. Among the range of complications that can occur following TJA, infection has proven to be a significant source of morbidity and mortality in its own right [6–9]. Numerous studies have examined the association between obesity and infection following TJA [10–13]. While the importance of these studies in ascertaining the importance of BMI as a potentially modifiable risk factor is acknowledged, there is a lack of a distinct threshold to be used in the preoperative period.

We conducted a systematic review to evaluate the threshold above which BMI is associated with SSI/PJI and found 17 studies meeting the inclusion criteria to answer this question. Most studies compared patients above and below BMI of 30 Kg/m^2 and limited their analysis to this dichotomous group. A recent meta-analysis examining the influence of obesity on complications following TKA concluded that patients with BMI ≥ 30 Kg/m^2 are at increased risk for infection [14]. Re-infection is also increased in obese patients who undergo revision for an infection of their primary or revised implant [13,15]. Lübbeke et al. [16] categorized patients into five groups based on their BMI levels in an attempt to specify which group had the highest risk for PJI. These investigators concluded that a BMI ≥ 35 Kg/m^2 should serve as a cutoff for increased risk for PJI. However, recent evidence suggests that a cutoff of 40 kg/m^2 [17,18] and even 50 kg/m^2 [19,20] should serve as the threshold above which the risk for PJI increases substantially.

The highest evidence to answer this question stems from two recent studies that used their large institutional databases (approximately 20,000 patients in each institution) to show a 10% increased risk for PJI for each BMI unit above normal (25 Kg/m^2) [17,18]. In both studies, the risk became progressively more pronounced for the group of patients with BMI values above 40 kg/m^2 with a three-times higher risk for SSI/PJI. The study by Shohat et al. [18] specifically aimed to determine whether there is a distinct BMI threshold above which the risk for infection increases substantially. The authors reported a linear increased risk with higher BMI with no distinct cutoff performing better than random chance.

To our knowledge there are no prospective randomized studies that directly address the subject of implementation of these BMI cutoffs (the majority of studies are retrospective reviews of databases or registries). While bariatric surgery did not seem to reduce complications following TKA, [21] it did show a reduction in complications after THA [22]. A recent systematic review of five studies with a total of 23,348 TJA patients showed no statistically significant difference in infection rates (superficial or deep) after bariatric surgery [23]. There are ongoing studies following obese patients undergoing bariatric surgery versus those who decline bariatric surgery, but no definitive conclusions are available on this subject at this time.

Our results suggest that the risk for infection increases gradually throughout the full range of BMI above 30 kg/m^2, and patients with a BMI above 40 kg/m^2 are at substantial (three-times) risk for infection. These results should encourage surgeons to encourage all overweight patients to reduce weight prior to surgery with a special emphasis on patients who have a BMI above 40 kg/m^2. Further studies should prospectively examine the influence of BMI reduction on reducing the risk for infection.

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QUESTION 6: Does bariatric surgery reduce the risk of surgical site infection/periprosthetic joint infection (SSI/PJI) in patients with obesity?

RECOMMENDATION: The evidence is inconclusive at present. Thus, preoperative bariatric surgery cannot be routinely recommended.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 85%, Disagree: 7%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

Obesity, defined as body mass index (BMI) > 30 kg/m^2, has reached alarming proportions in the United States (US), the United Kingdom (UK) and globally, with no signs of decline [1,2]. The national prevalence of obesity in US men and women from 2013 to 2014 has been reported as 35% and 40.4%, respectively [3]. In addition, it has been predicted that by 2025, 47% of men and 36% of women (aged between 21 and 60 years old) in the UK will be obese [2]. Obesity has also been linked to the development of osteoarthritis and joint disease [4]. As a result, a higher portion of obese patients will present to orthopaedic surgeons seeking total knee arthroplasty (TKA) or total hip arthroplasty (THA). George et al. reported that obese patients constituted 52% of THAs and 70% of TKA patients in 2011 [5].

Although obese patients can achieve high satisfaction and pain relief following arthroplasty [5], obesity has also been associated with increased risk of surgical site infection (SSI) and periprosthetic joint infection (PJI) [6–8]. As a result, obesity is viewed as a modifiable risk factor and the American Association of Hip and Knee Surgeons (AAHKS) workgroup on obesity concluded that the risks associated with a BMI > 40 kg/m^2 outweigh the functional benefit of an arthroplasty [9]. Therefore, many centers and providers will delay arthroplasty until the patient can reduce their weight below this threshold.

Bariatric surgery is often viewed as a safe, effective means to help morbidly obese patients achieve weight reduction [10]. It has also been shown to be more effective in helping patients reduce weight than nonsurgical methods [11]. Bariatric surgery is considered the most effective treatment for weight loss in patients with severe obesity, and it is indicated in patients with a BMI ≥ 40 kg/m^2 or patients with a BMI ≥ 35 kg/m^2 and at least one important comorbidity who have failed clinical management for weight loss [11,12]. Some orthopaedic surgeons advocate for bariatric surgery prior to hip, knee or ankle arthroplasty in order to lower the risk of postoperative SSI and PJI. Parvizi et al. demonstrated that patients who undergo bariatric surgery prior to total hip or knee arthroplasty experience significant functional improvements following surgery with an acceptably low complication rate [13].

Springer et al. described bariatric surgery as an effective and durable treatment for obesity. They reported that patients lost up to 50 to 70% of their excess weight (a BMI reduction of 10 to 15kg/m^2) following bariatric procedures [14]. However, there is limited evidence that supports that bariatric surgery is associated with reduced rates of SSI/PJI following total joint arthroplasty. Despite the lack of level I or level II evidence, nine retrospective studies have investigated the potential beneficial influence of bariatric surgery on SSI/PJI in obese patients undergoing total joint arthroplasty. The results are conflicting. Kulkarni et al. compared 90 patients who underwent bariatric surgery prior to total joint arthroplasty (TJA) to 53 patients who underwent bariatric surgery following TJA. They found that the infection rates following joint arthroplasty surgery were 1.1 to 3.7%, respectively. There was no statistical difference between the two groups (p = 0.55) [15]. In addition, six additional studies have demonstrated that undergoing bariatric surgery either prior to or after undergoing TJA does not influence the incidence of subsequent SSI/PJI [16–21].

Only two studies have demonstrated reductions of SSI/PJI in patients who underwent TJA following bariatric surgery [22,23]. One was a large cohort study using the Medicare database (bariatric prior vs. obese only patients, (odds ratio (OR) 0.36, 95% confidence interval (CI) 0.13 to 0.96, p = 0.049) [23] and the second used the New York State database (2.4% bariatric vs.1.3% obese TKA patients, p = 0.003, no difference for THA) [22]. Also, a meta-analysis published in 2015 demonstrated a reduction in postoperative infection in the bariatric group (OR 0.36, 95% CI 0.15 to 0.90, p = 0.03). However, no differences in infection were found when the results were stratified by superficial or deep infection [24]. The authors concluded that the analyses of postoperative complications following bariatric surgery were assessed as "very low" quality of evidence using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) approach. In addition, they reported very little confidence in these findings due to inconsistency, imprecision and the risk of bias. They concluded that bariatric surgery prior to hip or knee arthroplasty does not improve clinical outcomes or reduce complication rates for patients who are obese [24].

The existing literature has important limitations in attempting to answer the proposed question. Many of the aforementioned studies are retrospective in nature. There is a lack of prospective or randomized trials. There is also a lack of data on the nutritional status of obese patients undergoing bariatric surgery and TJA. This is important in that post-bariatric surgery patients may remain in a malnourished state following bariatric surgery [25]. Because malnutrition has been previously associated with an increased rate of PJI [26], the lack of data on the nutritional status of these patients prior to and after bariatric surgery can potentially confound results. The small sample sizes and the use of registry databases does not allow for subgroup analysis on the types of bariatric surgeries received. There are differences in weight loss and nutritional status between different types of bariatric surgery, and this may influence the rate of infection following arthroplasty [11]. In addition, the time interval between bariatric surgery and arthroplasty was often unreported or inconsistent across the different studies. In addition, given the relatively low rate of PJI in TJA, many of the current studies may be too underpowered to address this clinical question. Furthermore, the criteria for definition of SSI or PJI, particularly in the large database studies, were not consistently reported.

In conclusion, in the absence of strong evidence and a lack of studies with detailed data pertinent to the subject, we feel that subjecting obese patients to bariatric surgery prior to TJA for the sake of reducing subsequent SSI or PJI is not warranted.

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QUESTION 7: Does human immunodeficiency virus (HIV) predispose patients to surgical site infection/periprosthetic joint infection (SSI/PJI)? If so, what optimization should be undertaken prior to operating on patients with HIV?

RECOMMENDATION: Human immunodeficiency virus (HIV) infection is known to be a risk factor for surgical site infection (SSI) and periprosthetic joint infection (PJI). However, in patients who are medically optimized, with highly active antiretroviral therapy (HAART), the magnitude of the risk is small and comparable to HIV-negative patients. Patients must be optimized for underlying conditions including malnutrition, renal and liver disease, cluster of differentiation (CD4) count and viral load.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 96%, Disagree: 2%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

HIV has led to more than 70 million people currently infected and about 35 million HIV-related mortalities. An estimated 0.8% of adults aged 15 to 49 years worldwide are living with HIV [1]. Between 1979 and 1985, many hemophilic patients were exposed to HIV through administration of unscreened blood products [2]. The advent of HAART in 1997 changed the nature of HIV infection from a life-threatening condition into a well-controlled chronic disease, with patients achieving a near normal lifespan [3–8]. As the HIV-infected population ages, these patients may develop advanced age-specific morbidities such as degenerative joint disease [3]. Therefore, the demand for total joint arthroplasty (TJA) in HIV-infected patients is on the rise and concerns about proper treatment strategies and the outcomes of this procedure in this patient population are emerging [2,3,9,10].

Studies performed before initiation of HAART have reported infection-related complication rates as high as 50% [2,9,11]. These patients, in most cases, were hemophiliacs who had been co-infected with HIV [12] or had comorbidities such as intravenous drug abuse [13]. Later studies on HIV-infected patients without hemophilia had better outcomes and lower rates of periprosthetic joint infection (PJI), even equal to a healthy population [6–8,14–17]. This inconsistency in the literature reflects small sample sizes and the inclusion

TABLE 1. Demographics of representative studies on PJI in patients with HIV, but not hemophilia

Study	TJA Number	PJI Number	Number of Patients	Number of Male Patients	Mean Follow-Up	Mean Age (Years)
Capogna [8] 2013	69	3	57	Unclear (Only 58% of HIV cases presented)	609 days	44.8
Chokotho [15] 2013	15	0	12	Unclear – HIV patients not separated	Unclear	47.1 (not useable)
Cummins [7] 2014	8	0	7	3 (Not useable as operations not clear)	25 months (1–68 months)	35 (not useable)
Graham [6] 2014	43	0	29	19	3 years, 6 months (5 months–8 years and 2 months)	47 years, 7 months (21–59 + 5 months)
Joon Yoo [18] 2010	5	0	3	3	16.6 months (4–37 months)	38.6 (not separated by operation)
Lin [19] 2014	22	2	20	20	4.6 years (2–8.6 years)	49 (+/-17.8)
Lubega [14] 2009	18	0	18	Unclear	Unclear	52 (not useable)
Mahoney [20] 2005	54	1	40	31	2.3 years (1–7 years)	44.4 years (+/-9.3)
Snir [21] 2014	41	1	31	22	33 months (4–116)	49.6 (32–75)
Tornero [22] 2012	18	0	13	11	3.3 years (+/- 2.5)	44.3 (+/- 9.1)
Wang [23] 2012	8	0	5	Unclear	38.6 months (4–84)	44.5 (36–54)
Falakassa [24] 2014	32	0	24	17	14 months (1.5–60)	50 (31–74)
Issa [25] 2013	44	2	34	23	7 years (4–11 years)	48 (Range 34–80)
Lehman [13] 2001	4	0	NA	NA	Unclear	Unclear
Issa [16] 2017	50	0	45	31	6 years	57 years (38–72)

HIV, human immunodeficiency virus; NA, not available; PJI, periprosthetic joint infection; TJA, total joint arthroplasty.

TABLE 2. Demographics of representative studies on PJI in patients with HIV and hemophilia [3]

Study	TJA Number	PJI Number	Number of Patients	Number of Male Patients	Mean Follow-Up	Mean Age (Years)
Goddard [26] 2010	17	1	16	Unclear	9.2 years (2–23)	43 (25–70)
Haberman [27] 2008	?53	?	41	37	81 months (2–14 years)	46 (34–68)
Hicks [12] 2001	91	17	Unclear	Unclear	5.7 years (0.1–20.8)	39 (22–60)
Lehman [13] 2001	18	3	14	Unclear	62 months (24–152)	33 (25–48)
Norian [28] 2002	40	4	29	Unclear	110 months (24–246)	33.7 (+/-8.2)
Thomason [29] 1999	12	4	12 (not useable)	Unclear		Unclear
Powell [30] 2005	30	3	19	19	80 months (2–323)	33 (20–61)
Ragni [31] 1995	34	8	34 (not useable)	Unclear	Unclear	36 (+/- 3.1)
Rodriguez [32] 2011	21	2	21	Unclear	8.5 years (1–13)	36.5 (24–52)
Rodriguez [33] 2007	19	1	19	Unclear	7.5 years (1–10)	31 (24–42)
Unger [34] 1995	26	0	15	Unclear	6.4 years (1–9)	33 (25–42)

HIV, human immunodeficiency virus; PJI, periprosthetic joint infection; TJA, total joint arthroplasty.

of confounding conditions such as hemophilia, which in itself increases complication risks, and the use of HAART [11]. (Table 1 and Table 2 consist of most representative papers describing demographics and PJI rates in HIV-infected patients without hemophilia and with hemophilia, respectively) [3].

Confounding Factors (e.g., Hemophilia and Intravenous Drug Use)

There are conditions that have a strong effect on joint arthroplasty outcomes in HIV-infected patients. Lehman et al. analyzed data on 41 hip and knee arthroplasties performed on intravenous drug users, some of whom were HIV-positive, and they showed that drug use was an independent risk factor for infection after total joint arthroplasty [13]. This study and similar other studies have shown that comorbidities in patients, particularly hemophilia and intravenous (IV) drug abuse, are potential independent risk factors for developing PJI [13,26,33,35–38]. Some of these patients also demonstrated minimal benefit from the use of HAART [12,13]. A thorough social history and urine toxicology should be obtained to screen for current IV drug users. Ongoing illegal drug abuse is a strong contraindication for elective TJA [39]. Nevertheless, factors such as nutritional status, liver and renal function, CD4 cell count and viral load (VL), are correctable and need to be addressed in the perioperative period in HIV-infected patients [3,40].

We identified 15 studies suitable for inclusion in a systematic review to answer the posed question for hemophiliac patients [12,13,19,28,41–44]. Eight of the studies had an HIV-negative comparator group [19,42,43]. There were 47 PJIs/SSIs in 332 arthroplasties (0.142, 95% CI:0.106 to 0.184).

The relative risk of PJI/SSI based on a combination of the seven studies with a control group was 170, (95% CI: 0.93 to 3.1) indicating that the risk was not significantly elevated in the HIV-infected hemophiliac arthroplasty patients compared to the HIV-negative hemophiliacs (see Fig. 1).

Features common to most of the above studies on hemophiliacs are small numbers of study patients and long periods of follow-up with inclusion of a large proportion of patients who received joint arthroplasties before the HAART era.

CD4 count

The importance of CD4 count and its relation to the severity of the infection in patients with HIV has been previously confirmed [45,46]. However, the optimal threshold for CD4 count in patients undergoing elective arthroplasty has not been established. Limited data has shown some association between CD4 count and PJI in HIV-positive patients. In a retrospective study with a mean follow-up of 10.2 years, Parvizi et al. [9] noted a PJI rate of 28.5% (6 out of 21) and showed a significant association between the immune status of the patient and the incidence of PJI. The CD4 count at the time of arthroplasty was not available for four of six of these patients. However, the CD4 count was significantly lower at an average 239 cells/ml at latest follow-up for patients with deep infection versus 523 cells/ml for the study population as a whole ($p < .001$).

In the field of orthopaedic trauma procedures, there is evidence that patients with CD4 cell counts less than 200 have higher rates of complications than patients with higher counts. Other studies showed that risk factors for wound infection in the orthopaedic trauma setting include HIV clinical category B, CD4 counts of < 500 cells/ml, contaminated wounds and low serum albumin [47–49].

Viral load

The viral load, that is the number of copies of viral RNA in a patient's blood, is another test used to monitor HIV infection. It remains to be seen if the level of viral load can be used to predict the rates of PJI in HIV-positive patients who undergo TJA [3]. Horberg et al. [50] found that in HIV-infected patients undergoing surgical

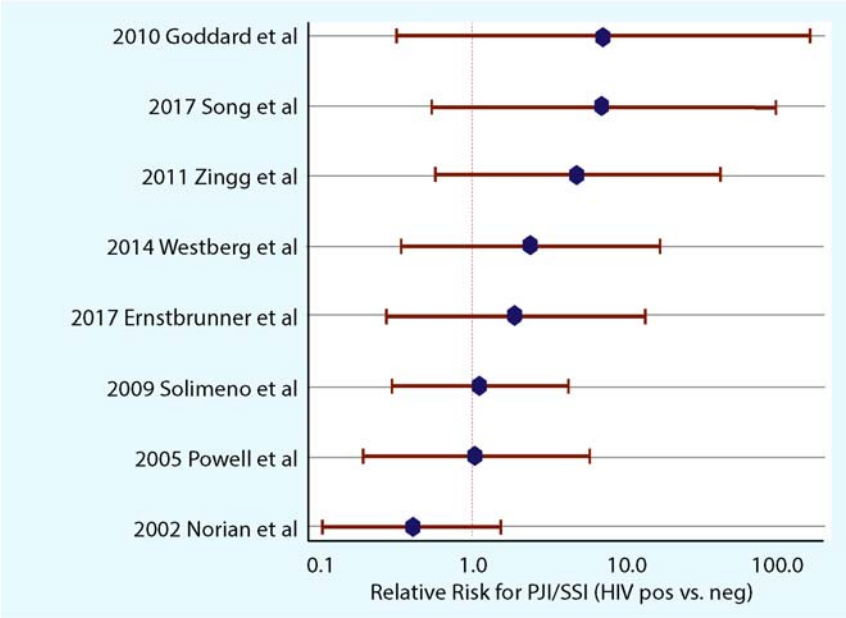

FIGURE 1. Forest plot of relative risk of PJI/SSI in HIV-infected hemophiliacs vs. HIV-negative hemophiliacs.

procedures (including both orthopaedic and non-orthopaedic procedures), HIV viral loads of > 500 copies/mL were associated with minimal complications, whereas HIV viral loads of > 30,000 copies/mL were associated with an increased risk of complications. If CD4 counts are > 400 cells/ml with undetectable viral loads, the patient might benefit from TJA as the risk of PJI may be decreased [51]. In a retrospective study, Falakassa et al. [24] suggested that well-controlled HIV patients on HAART therapy with undetectable viral loads and CD4 > 200 are at similar risk of PJI as the average population. Based on some indirect evidence, a CD4 count of > 400 cell/ml and a viral load of < 50 copies/ml could be ideal thresholds for elective TJA [50].

HAART

HAART therapy reduces HIV transmission, restores immune function, reduces HIV- related morbidity and mortality and improves survival [39,48]. Some studies have shown that HAART therapy could stabilize CD4 count within normal limits which is assumed to be correlated with better outcomes in patients undergoing orthopaedic procedures [39].

In a systematic review, Enayatollahi et al. [3] suggested that HIV-positive patients who are medically optimized with HAART and controlled for their comorbidities have an acceptable rate of PJI after TJA that approaches that of HIV-negative patients.

Malnutrition, Liver and Renal Disease

Malnutrition is strongly associated with a multitude of complications following TJA, including prolonged hospitalization, delayed wound healing, persistent wound drainage and subsequent susceptibility to infection. The nutritional status is assessed by the level of serum albumin (normal 3.5 to 5 g/dl), serum transferrin (normal 204 to 360 mg/dl), serum prealbumin (normal 15 to 35 mg/dl) and total lymphocyte count (800 to 2,000/ml) [49]. Although thresholds for these tests have not been established, any deviation of these parameters might be associated with increased complications. It is reasonable to expect that HIV-positive patients may suffer a higher risk of postoperative complications due to underlying malnutrition [52], abnormal weight loss, fluid and electrolyte imbalance and renal disease [10,11,19,43,53].

Using a nationwide database between 2005 and 2012, Kildow et al. [53] concluded that HIV-positive patients co-infected with hepatitis C virus (HCV) or hepatitis B virus (HBV) are at increased risk of PJI at two years, and the risk of revision after total hip arthroplasty is also increased at 90 days and 2 years.

Conclusion

The advent of HAART has transformed HIV infection to a well-controlled chronic disease and HIV-positive patients are expected to have a near normal life span. Elective arthroplasty is a safe procedure and could benefit this patient population should they be medically optimized with HAART and establish appropriate CD4 count and viral load, while addressing their comorbidities including malnutrition, liver and renal disease, hemophilia and IV drug abuse in the perioperative period.

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QUESTION 8: Do immunomodulatory disease-modifying medications (e.g., methotrexate or antitumor necrosis factor (anti-TNF) agents) need to be withheld preoperatively to reduce the risk for subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION:

1. For adults with inflammatory arthritis (rheumatoid arthritis (RA), psoriatic arthritis (PsA), adults with juvenile idiopathic arthritis (JA), ankylosing spondylitis (AS) or systemic lupus erythematosus (SLE)), all biologic anti-rheumatic medications including TNF inhibitors and IL-6 blockers (see Table 1 for complete list) should be withheld for a full dosing cycle prior to total hip (THA) and total knee arthroplasty (TKA), and the surgery should be timed to the week following the withheld dose. These medications can be restarted no less than two weeks after surgery if the wound is healing well, all sutures are out and there are no non-surgical site infections.
2. For adults with inflammatory arthritis or SLE, synthetic disease-modifying anti-rheumatic drugs (DMARDs; see Table 1), including methotrexate, can be continued through the perioperative period.
3. For adults with severe SLE, immunomodulatory medications (see Table 1) can be continued through the perioperative period.
4. For adults with mild SLE, immunomodulating medications (with the exception of tacrolimus) should be withheld prior to surgery and restarted at a minimum of 14 days after surgery if the wound is healing well and all sutures are out and there is no surgical site or non-surgical site infection.
5. For adults with RA, SLE, AS, PsA and JIA receiving glucocorticoids (GCs) for treatment of their rheumatic disease, who did not receive GCs during development and are not receiving replacement therapy, we recommend that the usual daily GC dose be given on the day of surgery rather than supra-physiologic ("stress dose") GCs.

LEVEL OF EVIDENCE: Limited, based on moderate to low-quality indirect evidence

DELEGATE VOTE: Agree: 87%, Disagree: 3%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

While arthroplasty provides important benefits for those with inflammatory arthritis and SLE, these patients are at increased risk of complications including infection [1–3]. To provide guidance, the American Association of Hip and Knee Surgeons (AAHKS) and the American College of Rheumatology (ACR) convened a panel of stakeholders including rheumatologists, orthopaedists, patients, infectious disease experts and methodologists. We systematically reviewed the relevant literature in Embase (1974 +), the Cochrane

TABLE 1. Medications included in this guideline

DMARDs: CONTINUE these medications through surgery.	**Dosing Interval**	**Continue/Withhold**
Methotrexate	Weekly	Continue
Sulfasalazine	Once or twice daily	Continue
Hydroxychloroquine	Once or twice daily	Continue
Leflunomide (Arava)	Daily	Continue
Doxycycline	Daily	Continue
BIOLOGICS: STOP these medications prior to surgery and schedule surgery at the end of the dosing cycle. RESUME medications at minimum 14 days after surgery in the absence wound healing problems, surgical site infection or systemic infection.	**Dosing Interval**	**Schedule Surgery (relative to last biologic dose administered)**
Adalimumab (Humira) 40 mg	Every 2 weeks	Week 3
Etanercept (Enbrel) 50 mg or 25 mg	Weekly or twice weekly	Week 2
Golimumab (Simponi) 50 mg	Every 4 weeks (SQ) or Every 8 weeks (IV)	Week 5 Week 9
Infliximab (Remicade) 3 mg/kg	Every 4, 6 or 8 weeks	Week 5, 7 or 9
Abatacept (Orencia) weight-based 500 mg; IV 1000 mg; SQ 125 mg	Monthly (IV) or weekly (SQ)	Week 5 Week 2
Rituximab (Rituxan) 1000 mg	2 doses 2 weeks apart every 4-6 months	Month 7
Tocilizumab (Actemra) IV 4 mg/kg; SQ 162 mg	Every week (SQ) or Every 4 weeks (IV)	Week 3 Week 5
Anakinra (Kineret) SQ 100 mg	Daily	Day 2
Secukinumab (Cosentyx) 150 mg	Every 4 weeks	Week 5
Ustekinumab (Stelara) 45 mg	Every 12 weeks	Week 13
Belimumab (Benlysta) 10 mg/kg	Every 4 weeks	Week 5
Tofacitinib (Xeljanz) 5 mg: STOP this medication 7 days prior to surgery.	Daily or twice daily	7 days after last dose
SEVERE SLE-SPECIFIC MEDICATIONS: CONTINUE these medications in the perioperative period	**Dosing Interval**	**Continue/Withhold**
Mycophenolate	Twice daily	Continue
Azathioprine	Daily or twice daily	Continue
Cyclosporine	Twice daily	Continue
Tacrolimus	Twice daily (IV and PO)	Continue
NOT-SEVERE SLE: DISCONTINUE these medications in the perioperative period.	**Dosing Interval**	**Continue/Withhold**
Mycophenolate	Twice daily	Withhold
Azathioprine	Daily or twice daily	Withhold
Cyclosporine	Twice daily	Withhold
Tacrolimus	Twice daily (IV and PO)	Continue
Dosing intervals obtained from prescribing information provided online by pharmaceutical companies. *2016 American College of Rheumatology/American Association of Hip and Knee Surgeons Guideline for the Perioperative Management of Anti-rheumatic Medication in Patients with Rheumatic Diseases Undergoing Elective Total Hip or Total Knee Arthroplasty		

IV, intravenous; SQ, subcutaneous; PO, oral
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Library and PubMed (mid-1960s +) from January 1, 1980 through March 6, 2016 and synthesized the evidence, reaching consensus on the recommendations listed above, to balance the risk of infection against the risk of disease flare [4]. An additional literature search was conducted from March 1, 2016 through February 28, 2018 and additional relevant articles were added to this discussion.

For synthetic non-biologic DMARDs there is evidence from randomized controlled trials revealing no increase in infection when these medications are continued through the perioperative period. Although there are no surgical trials directly comparing infection and flare for biologic anti-rheumatic medications including TNF inhibitors and IL-6 blockers, there are numerous trials that demonstrate an increase in infection associated with these medications in non-surgical settings. Because patients with mild SLE can be carefully monitored after surgery and medications can be restarted for flares, we recommend withholding all immunomodulating medications at the time of surgery. For patients with severe or potentially life or organ-threatening SLE, perioperative complications may be linked to active disease, so we recommended continuing immunomodulating medications through surgery, in consultation with the patient's rheumatologist.

Tofacitinib is a unique oral immunomodulator that increases infection risk, so we recommended withholding tofacitinib for seven days prior to surgery. Immunocompromised status is linked to high-dose biologic therapy, so we based the period of drug withholding on the dose interval, to reflect the period of effective immunosuppression that is not reflected in the serum pharmacokinetic half-life. For example, rituximab has a serum half-life of 18 to 32 days, yet B-lymphocyte depletion may persist ≥ 6 months after an infusion. This suggests that the optimal time for surgery is at the end of the dosing cycle at the drug immunosuppressive nadir.

Glucocorticoids (GCs) are typically administered at supraphysiologic doses ("stress-dose corticosteroids") to patients receiving long-term GCs at the time of THA and TKA, despite the consistent association with increased infection, out of concern for hemodynamic instability. Based on randomized control trials as well as observational studies that do not demonstrate hypotension when usual dose GCs are administered, we recommended continuing the usual dose rather than "stress-dose corticosteroids." This recommendation applies only when the GCs are given for a rheumatic conditions and not to those who received GCs during development or those receiving GCs as replacement therapy for other medical conditions.

Since this publication, the background assumption of increased infection risk for patients with RA has been confirmed in a large registry-based THA/TKA cohort study of 3,913 patients with RA compared with 120,499 patients with osteoarthritis (OA) [5]. Patients with RA had an increased risk of PJI (subhazard ratio (SHR): 1.46, 95% confidence interval (CI) 1.13 to 1.88). Biologics were administered within 90 days of surgery in 345 of 1,946 patients but did not increase the risk of PJI (SHR: 1.61, CI 0.70 to 3.69). A second retrospective cohort study analyzed surgeries in 4,288 patients with inflammatory bowel disease and inflammatory arthritis on chronic infliximab who received an infusion within 6 months of THA and TKA [6]. Exploiting the precision of infusion billing records, they determined that infliximab when given within four weeks of surgery compared to infliximab given > six months prior to surgery did not increase the risk of serious infection within 30 days after surgery (odds ratio (OR): 0.90, CI 0.60 to 1.34) or PJI within one year (OR: 0.98, CI 0.52, 1.87). Glucocorticoid dose > 10 mg significantly increased the risk of 30 day infection (OR: 2.11, CI 1.30 to 3.40) and PJI (HR: 2.70, CI 1.30 to 5.60). In a retrospective case control study using data from a large commercial database, 55,861 patients with OA or RA undergoing arthroplasty were identified, including 1,127 infected TJA cases that were matched to 1,106 controls. RA patients were 47% more likely to have a postoperative infection than OA patients (OR: 1.47, CI 1.04 to 2.08). Use of perioperative immunosuppressive medications did not increase the risk (OR: 1.12, CI 0.84 to 1.50). Perioperative prednisone use was again found to be a significant risk factor for infection (OR: 1.59, CI 1.28 to 1.97) [7].

These observational studies indicate that addressing infection risk for rheumatic disease patients remains important, and support our recommendation to give the usual dose of GCs, not supraphysiologic doses, at the time of THA and TKA. While biologics were not a risk factor for infection after surgery, unmeasured confounders may play a role in observational studies. These studies provide further justification for needed research in the future.

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QUESTION 9: Does liver disease (hepatitis C, cirrhosis, etc.) predispose patients to surgical site infection/periprosthetic joint infection (SSI/PJI)? If so, what optimization should be undertaken prior to operating on patients with liver disease?

RECOMMENDATION: Yes. Patients with liver disease such as hepatitis or cirrhosis have a higher risk of infection. These patients are at increased risk of intraoperative and postoperative bleeding. All efforts should be made to ensure such complications are minimized.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Hepatitis C virus (HCV) affects more than 185 million people worldwide, and approximately 80% of infected individuals progress to chronic infection, with 20% developing cirrhosis within 25 years [1–4]. As medical therapy continues to improve the life expectancy of patients with liver disease, there is an increasing demand for orthopaedic procedures in this population [5–8]. Earlier studies evaluating postoperative complications in this patient population were of small sample sizes and were not conclusive [6,9,10]. However, recent studies have predominantly demonstrated that, indeed, SSI and PJI occur at much higher rates among these patients [11].

PJIs can occur at a higher frequency among patients with liver cirrhosis compared with those without liver cirrhosis undergoing elective knee arthroplasty (2.7 vs. 0.8%), elective hip arthroplasty (3.66 vs. 0.69%) and hip fracture patients (6.30 vs. 1.10%), as shown by Jiang et al. by analyzing the data from the Nationwide Inpatient Sample and the State Inpatient Database. The study found that liver cirrhosis was an independent risk factor for PJI (odds ratio (OR): 2.4, confidence interval (CI) 1.87 to 3.12), as was a diagnosis of HCV without cirrhosis (OR: 2.3, CI 1.97 to 2.76) [5]. Another retrospective cohort study of primary total hip arthroplasty (THA) or total knee arthroplasty (TKA) patients within the Danish National Patient Registry also supported a higher rate of PJI within one year of surgery in patients with liver cirrhosis [12]. It is important to note that HCV itself may increase complication rates even in the absence of liver cirrhosis.

Pour et al. observed an increased rate of surgical complications, including PJI, in patients with non-cirrhotic HCV undergoing THA but not TKA [10]. The study by Issa et al. included 6,343 patients with HCV and 19,029 matched controls and demonstrated an increased rate of early postoperative surgical complications following THA or TKA in patients with chronic HCV [6]. The cohort also had a higher rate of 90-day complication and readmission [13]. Best et al. used the National Hospital Discharge Survey to compare 26,444 patients with HCV undergoing THA or TKA with a control cohort of 8,336,882 patients without HCV. They reported higher rates of PJI in patients with HCV undergoing total joint arthroplasty (TJA) (HCV: 0.84%, controls: 0.09%, OR: 9.5, CI 8.3 to 10.8) [14]. Studies by Cancienne et al. using the PearlDiver patient record database showed significant OR of 1.7 to 2.1 for infection in total knee, hip [15] and shoulder [16] arthroplasty at 3, 6 and 12 months after surgery. These 3 groups had respectively 15,383, 8,380 and 1,466 cases with HCV that were compared to, respectively 146,541, 48,440 and 21,502 matched control patients. Kildow et al. have demonstrated that by matching control group with age, gender and Charlson comorbidity index (CCI), patients with HCV had higher rates of complications in a 30-day, 90-day or two-year period after TJA [17].

In addition, hepatitis B virus has been recognized as an independent risk factor for PJI after total knee arthroplasty [18]. The risk of PJI at 90 days and two years after total hip and knee arthroplasty were also significantly increased [17]. As compared to control patients, those with liver cirrhosis have more blood loss, higher complications and higher mortality rates. Among cirrhosis patients, alcohol-related cirrhosis carried the highest rate of perioperative complications [19,20].

There are several different explanations for the higher PJI risk in liver cirrhosis patients. One explanation is that liver disease may impair platelet function and cause thrombocytopenia that increases the risk of intraoperative and postoperative bleeding [21–23]. HCV could suppress the immune system, damage the endothelial cells, and lead to severe medical and surgical complications [6,24,25]. Intraoperative blood loss and the need for concentrated red blood cell transfusions reduce the immunological condition of these patients even further. Moreover, the formation of a hematoma around the surgical wound in the days following the intervention is yet another risk factor for developing a PJI. Also, patients with HCV may have beta-islet cell dysfunction and subsequently may develop diabetes mellitus that may result in an increased prevalence of wound complications and the potential for infection [21]. Also, another possible reason is that patients with liver disease had a decreased ability to activate the reticuloendothelial system, lymphoproliferation, neutrophil mobilization and phagocytic activity, all of which diminish their bactericidal activity and have been suggested as important contributing factors to this predisposition towards bacterial infection [16,26,27].

Orthopaedic surgeons should be increasingly aware of this association which should influence the shared decision-making process of performing TJA in patients with liver disease [12,20]. We believe that it is in these patients that preventative measures should be heightened against infection and that strict postoperative control should be followed to proceed aggressively if the infection is suspected. The hemostatic balance should be corrected before surgery according to established procedures such as vitamin K administration or concentrated plasma transfusions to avoid excessive bleeding or perhaps patients with advanced stage of disease should not subject to elective arthroplasty [28,29]. Also, the immune-compromised status of patients with liver disease should be more stringently monitored before surgery [26].

After correlating the seroprevalence rate and underdiagnosed rate, Cheng et al. have concluded that routine screening for HCV infection is not cost-effective [30]. The other study made the same conclusion by comparing the cost and the transmission rate of HCV through percutaneous contact with blood [31].

Given the presence of overwhelming evidence in the literature, we conclude that liver disease such as hepatitis or cirrhosis predisposes patients to SSI/PJI. The hemostatic balance and immune

compromised status should be corrected before surgery in patients with liver disease. There are presently no proposed guidelines to better prepare patients with liver disease for orthopaedic surgery. Future research should address care optimization for these patients. Hepatitis will increase the rate of complication after elective arthroplasty. The advantage of operation and disadvantage of possible complications should be carefully evaluated and discussed with the patient.

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QUESTION 10: Is there a link between opioid consumption and an increased risk for surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Yes. The utilization of opioids prior to surgery has been associated with an increased risk of developing SSIs/PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 71%, Disagree: 17%, Abstain: 12% (Super Majority, Strong Consensus)

RATIONALE

In both in vitro studies and in animal models, opioids have been shown to have immunosuppressive effects, modulating both the adaptive and innate immune systems [1–6]. Opioids have been implicated in the development of various infections including human immunodeficiency virus (HIV), hepatitis C virus (HCV) and opportunistic bacterial infections [4,5,7,8].

Despite the increased interest in opioid research, few studies within the arthroplasty literature have examined the effect of preoperative opioid consumption and the subsequent development of infection. With respect to surgical site infections, Menendez et al. found that preoperative opioid utilization was associated with higher patient morbidity, including an increased risk of surgical site

infections [9]. For PJI, Cancienne et al. found in a national database review that preoperative narcotic use was associated with a higher risk of PJI within one year [10]. Similarly, Bell et al. reported in a retrospective case-control study that preoperative opioid usage was independently associated with an increased risk of PJI within two years [11]. Furthermore, preoperative opioid usage has been implicated as a risk factor for early revision surgery [12–14]. Neither of the two database surveys in the literature, however, performed further subanalyses on type of revision. Therefore, the relationship between preoperative opioids and septic revisions remains unknown.

In conclusion, limited evidence exists to support the role of opioids as a risk factor for development of SSI/PJI. Given the scope of the danger posed by these medications, there is a need for further studies to develop more concrete recommendations for potential risk factor modification.

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QUESTION 11: Does the presence of anxiety/depression and mood disorders increase the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs)? If so, what are the considerations that should be implemented to reduce the risk of SSIs/PJIs?

RECOMMENDATION: There is emerging evidence to suggest that affective disorders, such as depression and anxiety, increase the risk for PJIs. Although both physiological and psychological explanations for this association have been offered, it is not clear whether modulating or treating these disorders prior to surgery results in a reduction in the risk of PJIs.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 88%, Disagree: 4%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

Recent studies suggest that affective disorders, such as depression and anxiety, can increase the risk for SSIs/PJIs [1]. There are both physiological and psychological reasons for this association. Depression has been shown to stimulate production of pro-inflammatory cytokines, such as IL-6, as well as promote the down-regulation of the cellular immune response (natural killer cell activation and T-helper cell replication) [2,3]. Promotion of IL-6 stimulates the secretion of corticotrophin-releasing hormone (CRH), which increases the production of plasma adrenocorticotropic hormone (ACTH) and cortisol, and thus inhibits certain aspects of the immune response [2,4]. Patients with depression and anxiety disorders are also likely to suffer self-neglect, that places them at higher risk of SSI/PJI [5,6]. Patients with affective disorders are likely to be smokers, suffer from malnutrition and consequently can be anemic, consume alcohol or live in social isolation, all of which places them at higher risk of SSIs/PJIs [7–12].

While the link between depression and PJI still warrants investigation, depression has been shown to be an independent risk factor for PJI following primary TJA in several national registry studies [13–16]. Browne et al. reported the incidence of depression in the arthroplasty population to be 10.0% [14]. This same study found depression to be associated with greater risk of postoperative infection (odds ratio (OR): 1.33) [14]. A case-control retrospective study by Bozic et al. found depression to be independently associated with an increased risk of PJI in total hip arthroplasty patients (hazard ratio (HR): 1.28) [17]. Similarly, another single center retrospective study of primary total hip arthroplasty (THA) found depression to be significantly related to PJI [18]. Furthermore, a systematic review and meta-analysis of 66 observational studies (23 prospective, 43 retrospective) pooled variably adjusted relative risks demonstrated depression produced a significantly increased risk of PJI (RR: 1.48, 95% CI 1.13 to 1.95) after total knee arthroplasty (TKA) or THA [19].

Other mental health disorders, such as bipolar disorder and schizophrenia, have also demonstrated an association with PJI. Kheir et al. demonstrated patients with psychosis and depression had increased odds of developing PJI at 90 days (OR: 3.334, p = 0.049), two years (OR: 3.94, p = 0.004) and at any time point (OR: 4.32, p = 0.002) [20]. Furthermore, Klement et al. demonstrated that patients with any psychiatric illness (bipolar disorder, depression and schizophrenia) undergoing elective primary TKA and primary THA, were at increased risk for PJI (TKA OR: 2.17, p < 0.001, THA OR: 2.26, p < 0.001) [15,16].

While there is substantial evidence that depression is an independent risk factor for PJI, there is limited evidence that controlling or treating depression results in a reduction or normalization of the PJI risk. A recent retrospective study of over 20,000 arthroplasty patients by Yao et al. demonstrated no association between the use of perioperative antidepressants and increased risk of revision or PJI; however, selective serotonin reuptake inhibitor (SSRI) users did experience lower risk of all-cause revision and aseptic revisions [21]. A retrospective study of 140 patients undergoing anterior cervical discectomy and fusion found similar self-reported surgical outcomes in patients pretreated with antidepressants for at least six months prior to surgery compared to the control group that had no prior history of depression [22]. However, future prospective interventional studies investigating the influence of depression treatment modalities on PJI risk in arthroplasty patients are warranted.

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QUESTION 12: Does vitamin D deficiency (VDD) increase the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing orthopaedic procedures?

RECOMMENDATION: Unknown. VDD may increase the risk of subsequent SSIs and/or PJIs in patients undergoing orthopaedic procedures by diminishing vitamin D-mediated innate and adaptive immune responses.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 82%, Disagree: 5%, Abstain: 13% (Super Majority, Strong Consensus)

RATIONALE

The exact mechanism of how vitamin D affects immune function is unknown. Numerous studies have demonstrated its regulation of both the innate and adaptive immune responses [1–6]. Vitamin D has been shown to activate the innate immune system to kill bacteria

through intracrine regulation of monocytes, as well as by modulating production of anti-microbial peptides (AMPs) and cytokines [1,2]. Vitamin D activates the adaptive immune response through paracrine regulation in dendritic cells, T cells and B cells [1].

Clinical evidence of VDD and risk of SSI/PJI in the orthopaedic literature is limited. In a prospective study, measuring serum 25-hydroxyvitamin D levels, VDD was found in 64% of patients presenting for primary total joint arthroplasty (TJA), 52% of patients presenting with aseptic loosening, and 86% of patients presenting with PJI – a statistically significant difference for PJI compared to the other groups [7]. A retrospective case-control study of revision TJAs had similar findings, with PJI patients being more likely to have VDD than patients being revised for aseptic indications (72.7 vs.48.4%, respectively) [8]. Additionally, prevalence of VDD was 55% in the revision TJA population compared with 39% in the primary TJA population. Importantly, when controlling for other nutritional parameters such as albumin and transferrin, VDD remained predictive of PJI as the reason for revision surgery [8].

To date, there are no clinical studies on the effect of vitamin D supplementation and the risk for SSI/PJI. In a PJI mouse model, VDD mice were shown to have an increased bacterial burden when compared to VDD mice that received "rescue" vitamin D supplementation [9]. Bacterial burden was similarly decreased between normal mice and the VDD "rescue" mice receiving supplementation.

VDD is common, with rates reported to be 42% in adults in the United States, and 24 to 65% in TJA patients [10–14]. As a potential modifiable risk factor for SSI and PJI, VDD is an important area for future study.

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QUESTION 13: Is preoperative anemia a risk factor for surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Based on available evidence, preoperative anemia, as defined by a hemoglobin of less than 13.0 g/dl in men and 12.0 g/dl in women, is an independent risk factor for postoperative SSI/PJI following total joint arthroplasty (TJA).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 89%, Disagree: 8%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Anemia is a common condition that is estimated to manifest in 21 to 35% of patients who present for primary TJA [1,2]. Anemia often presents as part of a spectrum of comorbidities and is difficult to study in isolation. However, recent literature demonstrates a link between postoperative complications and preoperative anemia in several published studies [3–13]. The majority of the orthopaedic literature focuses on TJA with one study investigating preoperative anemia in relation to total ankle arthroplasty (TAA) [14].

One of the most devastating complications following TJA is that of PJI or SSI and as the number of arthroplasties performed annually continues to increase, prevention will be paramount. Although rare, this devastating complication represents an increase in morbidity and mortality as well as a important economic burden [4,13,15]. Several documented patient-related risk factors exist for increased incidence of PJI including rheumatological disease, diabetes and obesity [4,16]. In some instances, preoperative optimization of these

chronic diagnoses can lead to favorable risk modification preoperatively [16]. Preoperative anemia, most commonly defined by the World Health Organization (WHO) by a hemoglobin value of less than 13.0 g/dL in men and 12.0 g/dL in women, is one such risk factor that has been evaluated and found to be an independent predictor of postoperative complications including PJI [2,4,5,10,11,17,18].

A compelling study to this end is a retrospectively collected, case-controlled study that demonstrates patients who have preoperative hemoglobin values of less than 13.0 g/dl in men and 12.0 g/dl in women had a higher overall rate of complications (odds ratio (OR): 2.11) than their matched counterparts [11]. The cohort consisted of 2,576 (19%) patients who had anemia matched to 10,987 patients with lab values within normal limits. After controlling for other significant comorbidities, the rate of overall complications for the anemic cohort was 33.2% as compared to 15.4% in the non-anemic cohort. Pertinent to the present discussion, the rate of infection was 4.5% in the anemic patients compared to 1.12% in the non-anemic patients (OR: 2.83, 95% confidence interval (CI) 1.78 to 4.51; $p < 0.0001$) [11].

A pair of level II studies by Bozic et al., based on administrative data within a Medicare population, revealed an Adjusted Hazard Ratio for anemia in TJA to be 1.36 and 1.26 respectively ($p = 0.0347$ and $p = 0.0014$) [17,18]. In a level III study specifically investigating the relationship between preoperative anemia and PJI, Greenky et al. reported that anemia was independently associated with an adjusted odds ratio of 1.95 (1.38 to 2.56) for the risk of PJI postoperatively [5].

Swenson et al. reviewed an institutional series of patients with confirmed PJI and demonstrated that preoperative anemia in this setting leads to decreased success of open debridement and polyethylene exchange [10]. They demonstrated an odds ratio of 6.7 (CI 2.2 to 22.4, $p = 0.0013$) of failure in patients with preoperative anemia. Failure, they found, was exacerbated by a combination of infection with *Staphylococcus* species and preoperative anemia as patients that underwent irrigation and debridement absent these two factors had a 97.1% success rate as defined by maintenance of a well-fixed implant without the need for additional surgery or lifelong oral antibiotics [10].

The present data suggests with moderate certainty that patients with preoperative anemia are more likely to suffer from a periprosthetic joint infection postoperatively than those who undergo surgery and are not anemic. Although studies that draw this conclusion are few, they independently corroborate this conclusion in both large cohort administrative-based data and institutional registries. Although adjusted odds ratios from these studies vary (1.26 to 2.11), all demonstrate that a hemoglobin value below 13.0 g/dl in men and 12.0 g/dl in women is an independent risk factor for PJI [5,10,11,15,17,18].

It also remains unclear if the presence of preoperative anemia itself, regardless of management, is a risk factor or indeed if it is the treatment for anemia with allogeneic blood transfusion which conveys a risk. Preoperative anemia is also the greatest predictor of the need for blood transfusion even in the setting of routine tranexamic acid use [19–21] and allogeneic blood transfusion has been independently correlated to SSI/PJI [7,22,23]. Further research is needed into this area, preferably with robust, large scale, multicentered trials.

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QUESTION 14: What preoperative optimization for anemia can be done to increase the hemoglobin concentration?

RECOMMENDATION: Literature suggests that the administration of iron and/or erythropoietin (EPO) increases preoperative hemoglobin concentration and decreases the need for postoperative allogeneic blood transfusion. However, iron may only be effective for patients with pre-existing iron deficiencies and is associated with many side effects. Given the high costs of EPO, it's preoperative administration to avoid transfusion alone has not been found to be cost effective. Further research is required to assess the risks and benefits of preoperative allogeneic blood transfusion.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 3%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The current literature presents several strategies to increase preoperative hemoglobin including iron supplementation, human recombinant (EPO) injection and preoperative blood transfusion.

Recommended initial management is correction of any deficiencies (such as iron, folate, ferritin, B12, etc.). If patients are noted to be iron deficient, the hemoglobin level can be raised with iron alone, either intravenous (IV) or oral [1]. Oral iron is cheap but takes two to three months to work [2]. Oral iron formulations are also associated with a high gastrointestinal (GI) side effect profile. A 2015 systematic review and meta-analysis examined 43 randomized controlled trials (RCTs) comparing oral iron vs. IV formulations or placebos and found more GI side effects with oral vs. IV formulations (odds ratio (OR): 3.05), and oral vs. placebo (OR: 2.32). This increase in GI side effects in turn reduces compliance with treatment [3]. Intravenous iron is more expensive but may increase hemoglobin levels in two to four weeks depending on the pre-treatment hemoglobin level and the degree of iron deficiency. Side effects are few and generally mild, but rare cases of anaphylaxis are seen as documented by a systematic review which noted 8 cases out of 2,186 infusions [4].

The use of preoperative iron supplementation to raise preoperative hemoglobin for all patients, regardless of iron status, is a more controversial intervention. This is due to conflicting literature, side effects of treatment and ambiguity as to the length of treatment needed to achieve a demonstrable perioperative hemoglobin improvement. Cuenca et al. demonstrated that the use of preoperative iron supplementation, vitamin C and folate for 30 to 45 days before surgery resulted in lower transfusion rate in primary total knee arthroplasty (TKA) patients (5.8 vs. 32%) without existing hematological deficiencies [5]. A further study by Cuenca et al. from 2004 investigated the use of IV iron given on admission and prior to surgery for patients with femoral neck fractures, again without hematological deficiencies, vs. a control group. They concluded that IV iron resulted in a lower transfusion rate postoperatively [6]. However, a study by Lachance et al. refutes this point and showed no difference in the postoperative transfusion rates of total joint arthroplasty (TJA) patients who participated in iron supplementation for three weeks prior to surgery [7]. In addition, iron supplementation was again associated with high levels of side effects including constipation (33%), heartburn (13.8%) and abdominal pain (12.6%) [7]. One limitation of these studies is that none mention improvements of preoperative hemoglobin levels.

The preoperative administration of EPO has universally demonstrated an increase in preoperative hemoglobin and a decreased need for postoperative allogeneic blood transfusion, but with limitations. In a systematic review [8], eight studies (five RCTs and three cohort studies) were included in investigating the effects of preoperative EPO in conjunction with oral or IV iron in patients undergoing major orthopaedic surgery vs. various control groups [8]. After treatment, the mean preoperative hemoglobin was 14.3 ± 0.3 g/dl in the EPO cohort compared to the control (12.4 ± 0.4) [8]. EPO has also been shown in several studies, including randomized controlled trials, to decrease the postoperative rate of allogeneic transfusion [9] .

These studies demonstrate a significant decrease in allogeneic transfusion with EPO as compared to routine care [10–12]. Furthermore, in a meta-analysis spanning 26 trials and 3,560 participants, Alsaleh et al. showed that the preoperative use of erythropoiesis stimulating agents reduced allogeneic blood transfusion in patients undergoing hip and knee surgery (rate ratio (RR): 0.48, 95% confidence interval (CI) 0.38 to 0.60, $p < 0.001$) without an increased risk in the development of thromboembolism [13]. Additionally, the largest prohibitive factor for the use of EPO remains cost [14]. Bedair et al. performed a cost-analysis on preoperative use of EPO in TJA patients to avoid transfusion [14]. They demonstrated that the EPO strategy was more costly compared to no EPO (USD 2,632.00 versus USD 2,284.00) and its cost would need to be less than USD 225/dose for this to change. Similarly, in their RCT, So-Osman et al. reported that the cost per avoided blood transfusion in TJA when using EPO preoperatively was 7,300 euros or approximately 9,000 USD, with the authors concluding that this made EPO prohibitively expensive [9].

The combination of iron supplementation, EPO and tranexamic acid (TXA) has also been studied. Zhang et al. investigated the safety and effectiveness of optimized blood management for patients undergoing elective hip and knee arthroplasty by retrospectively comparing the use of TXA with and without the addition of iron supplementation and recombinant human erythropoietin [15]. This study demonstrated that the use of TXA, iron and EPO decreased total blood loss, the need for transfusion and hemoglobin drop without increasing the incidence of venous thromboembolism or mortality [15].

Another method described to increase preoperative hemoglobin is preoperative blood transfusion. A 2010 systematic review assessed four cohort studies, each with 100 patients or more, that compared preoperative autologous transfusion against usual care [8]. The results suggested that preoperative transfusions reduced the need for postoperative transfusions. However, there was no specific mention regarding the improvements in preoperative hemoglobin concentration, nor investigation into other clinical outcomes or adverse events that may be associated with blood transfusions [8].

In conclusion, there is limited evidence to suggest that routine administration of iron and preoperative transfusions increase preoperative hemoglobin and moderate evidence to suggest that EPO increases preoperative hemoglobin. Oral iron is useful in the setting of iron deficiency, but, when used routinely, it is not particularly effective and has a high rate of side effects, particularly gastrointestinal. EPO has routinely been shown to be more effective at increasing preoperative hemoglobin, but has a high monetary cost.

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QUESTION 15: Does an effort to increase preoperative hemoglobin concentration influence the rate of postoperative surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: Despite the absence of evidence demonstrating a reduction in SSIs/PJIs with optimization of preoperative hemoglobin, we recommend that all efforts be made to address and optimize anemia preoperatively.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 90%, Disagree: 4%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

With moderate evidence to suggest that preoperative anemia is associated with an increase in SSIs/PJIs and modalities exist to increase preoperative hemoglobin, the next logical step is to determine whether modification of this preoperative variable reduces the risk of SSIs/PJIs. However, no studies have investigated whether increasing preoperative hemoglobin decreases postoperative SSIs/PJIs. Studies have demonstrated that treatment of preoperative hemoglobin reduces postoperative transfusions [1], which have also been associated with PJIs [2–4], but the direct link between increased preoperative hemoglobin and decreased PJI/SSI reduction has not been established. This information would be important as it would help balance the potential benefits of preoperative iron treatments against the known risks and costs. Until evidence exists to suggest the administration of erythropoietin (EPO) and or iron supplementation safely decreases SSIs/PJIs, we cannot recommend their routine use in total joint arthroplasty for this purpose alone.

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1.3. PREVENTION: HOST RISK MITIGATION, LOCAL FACTORS

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QUESTION 1: Does a prior surgical procedure (with or without retained hardware) in the same joint as the arthroplasty increase the risk of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Open surgical procedures with or without the use of hardware increases the risk for subsequent SSI/PJI in the same joint receiving arthroplasty. We suggest that elective arthroplasty is delayed on the affected joint that has undergone a recent (within six months) major surgical procedure.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 6%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Violation of the joint capsule by previous surgery has been found to be associated with an increased risk of subsequent PJI and SSI. Berbari et al. [1] investigated patients undergoing total hip arthroplasty (THA) or total knee arthroplasty (TKA) after a prior capsular violation in a prospective case-control study and found a significantly increased risk for PJI (hazard ratio (HR): 1.74, 1.23 to 2.47, p = 0.002) and for SSI (HR: 1.66, 1.16 to 2.39, p = 0.006). The extent of the initial index injury or procedure influences infection risk. One study found that patients with a previous fracture had an increased risk of PJI/SSI (rate ratio (RR): 5, p = 0.04) compared to previous soft tissue injury after conversion to TKA. Furthermore, a significantly higher infection rate was seen in patients with a prior history of open reduction internal fixation (ORIF) (31%) versus arthroscopy (3.3%) [2].

Arthroscopy has been described as a valuable tool for treating mechanical symptoms related to early arthritis. However, there is no strong evidence to suggest that the risk for PJI is higher in patients with prior arthroscopy of the hip and the knee. Some national registry retrospective studies, as well as matched case-control studies, evaluated the outcomes of total joint arthroplasty (TJA) after knee arthroscopy. Regarding the risk of infection after arthroscopy, none of these studies noted an increased risk of subsequent PJI in these patients [3–7].

The latter studies did not, however, examine the time interval between arthroscopy and the index arthroplasty. It appears that the time interval between arthroscopy and TKA may be an important issue as demonstrated by Werner et al. in a cohort study of 681 patients from a national database. They noted an increased risk of infection with an odds ratio of 2 if the TKA was performed within six months of an arthroscopy [4]. On the contrary, Viste et al. [5] found no increased risk of infection or other complications if knee arthroscopy was performed within one year and the studies by Piedade et al. [8,9] again found no correlation between arthroscopy and TKA interval with complications and failures.

The literature is more limited with regards to hip arthroscopy. Haughom et al. examined 84 patients in a matched case control study and found 1 periprosthetic THA infection each in those with and without prior hip arthroscopy at a mean 3.3-year follow-up [10]. This was consistent with other similar studies evaluating outcomes of THA after hip arthroscopy [11–15]. There is no evidence regarding the safe time interval between the hip arthroscopy and THA in order to decrease the rate of possible subsequent PJI.

Another important surgical procedure that is often performed in the knee is anterior cruciate ligament (ACL) reconstruction. Some of these patients eventually develop arthritis and may undergo TKA. The question is whether TKA in this patient population may be associated with an increased risk for PJI. TKA outcomes after ligament reconstruction have been investigated by multiple authors [2,16–19]. A retrospective review of 64,566 primary TKA from the New Zealand Joint Registry concluded that prior major surgery had a two- to three-fold increase in risk of revision for PJI at both six months (p = 0.046) and one year (p = 0.01). Prior ligament reconstruction (odds ratio (OR): 2.04, 95% 0.75 to 5.53) or osteotomy (OR: 2.72, 95% 1.33 to 5.56) were especially associated with an increased risk of subsequent PJI [2]. Hoxie et al. retrospectively reviewed TKA following ACL reconstruction and found no incidence of PJI in their small series [16]. To the contrary, Watters et al. [18] found that patients with prior ACL reconstruction (excluding patients with a history of fracture or osteotomy) had a significantly higher incidence of PJI compared to those without prior ACL reconstruction (3.3% ACL group, 0% control, p = 0.04). The operative time for patients with prior ACL repair was significantly longer (p < 0.001) as well. Pancio et al. [19] highlighted a significantly increased risk for infection at 7% after multi-ligament reconstruction (> two ligaments) versus < 1% for those without prior ligament reconstruction (OR: 9, 95% confidence interval (CI) 1–78, p = 0.047). Increased risk for infection after arthroscopy in which ligament reconstruction is conducted may be explained by the presence of foreign material, longer operation time, poor soft tissue integrity, increased risk for arthrofibrosis as well as the need for increased surgical dissection because of prior surgery.

THA is the treatment of choice for patients with symptomatic osteoarthritis following prior femoroacetabular impingement (FAI) surgery. The results of THA after femoroacetabular osteoplasty (FAO) surgery including the incidence of PJI/SSI has not been well-studied. However, an ongoing study at the Rothman Institute has not detected an increased risk of complications, including infection, in over 50 patients with prior FAO who have undergone THA (pending publication).

Developmental dysplasia of the hip and rotational deformities of the hip are increasingly managed with periacetabular/rotational osteotomy in the younger population. These patients may eventually need THA due to progression of arthritis. Several studies have evaluated the outcomes and technical difficulties of THA after periacetabular osteotomy/rotational acetabular osteotomy (PAO/RAO), but only a few have addressed the potential for increased PJI/SSI in this patient population. Two matched cohort reviews of patients with prior acetabular osteotomy who underwent THA did not detect an increased risk for subsequent PJI compared to controls [20,21]. Thus, based upon the available data, it appears that conver-

sion of THA after prior arthroscopy, femorocacetabular osteoplasty or pelvic osteotomy do not appear to significantly increase the risk for subsequent PJI. One retrospective review of failed salvage hip procedures for osteonecrosis found no significant difference in the rate of PJI but detected an increased incidence of SSI (8.1%, p = 0.005), especially if the prior procedure was open (10%, p = 0.003), compared to patients with no prior surgery (0%) [22].

Fresh osteochondral allograft (OCA) transplantation is an effective treatment for osteochondral defects in the knee. However, many patients eventually require management with a TKA. The effects of prior OCA transplantation on TKA outcomes are not well-defined. Steinhoff et al. [23] retrospectively evaluated 39 TKA patients who had undergone prior OCA and found that the failure of TKA was markedly higher in this patient population at 31.4%. Of all 35 patients with at least one-year follow-up, 11 patients required a reoperation at 10 years, 2 due to infection (5.7%). These results are consistent with high failure rates (17.1%) reported by Morag et al. [24] in their case series of 35 TKAs after OCA, although no revisions were due to SSI/PJI. It appears that patients with multiple prior knee operation are more likely to experience poor outcomes following TKA including failure as a result of infection.

Retained hardware following previous open reduction internal fixation (ORIF) has been shown to increase the risk for subsequent PJI and SSI. Suzuki et al. [25] found an increased incidence of PJI in patients being converted to TKA with retained hardware (25%, OR: 26.0, CI 95% 4.5 to 151.0, p < 0.05) and previous ORIF (21%, OR: 7.9, CI 95% 1.1 to 57.1, p < 0.05). The authors suggested that compromised peri-incisional vascularity may contribute to risk of infection and they suggested the use of antibiotic cement or long-term antibiotics in this cohort of patients. However, another matched cohort study by Manrique et al. [26] did not achieve statistical significance in a similar patient population undergoing conversion to TKA. An increased incidence of SSI was seen in patients with prior hardware in situ (10.9%) versus no prior hardware (4.5%) (HR: 2.59, 95% 0.78 to 8.57, p = 0.12) [9].

Klatte et al. [27] retrospectively reviewed 124 patients undergoing TKA with prior history of knee surgery and pre-existing hardware. The investigators used a single-stage technique and reported one subacute infection seven months postoperatively. Similar outcomes were reported in an analogous THA patient population (109 patients, 1 infection) [28]. Archibeck et al. [29] conducted a retrospective study on 102 total hip arthroplasties (THAs) after failed internal fixation due to prior hip fracture, 12 (11.8%) of whom had early surgical complications related to the procedure, although only 50 patients were available at the two-year follow-up. The outcome of THA in patients with prior acetabular fracture has been reported to be inferior compared to primary THA [30–36]. Regarding PJI/SSI, the data is conflicting in these patients. However, a few case-control studies have reported higher rates of PJI after THA in patients with prior acetabular osteosynthesis [35,37,38].

Osteotomy is another joint preservation technique which may be employed in younger patients who are recalcitrant to nonoperative management. Nelson et al. [40] reviewed nine consecutive patients (11 knees) who had undergone varus osteotomy of the distal femur prior to TKA. Although no infections or wound complications were reported, functional and radiographic outcomes varied substantially, thereby demonstrating the increased complexity and inferior outcomes which can be expected with TKA in this population. Bergenudd et al. and Faralli et al. [41,42] demonstrated an increased risk for postoperative complications in TKA candidates following previous proximal tibial valgus osteotomy.

Removal of hardware (ROH) before TJA conversion may help to prevent PJI/SSI. When ROH after ORIF for closed intra-articular tibial plateau fractures was performed at least four months before conversion to TKA, no cases of deep infection were seen and only one diabetic patient developed a superficial infection and wound dehiscence [39]. A retrospective multicenter review evaluated the outcomes of TKA after medial opening wedge and lateral closing wedge high tibial osteotomy, in which 98.5% of patients had ROH performed. The incidence of infection was found to be 3.6% and the number of incisions needed for ROH did not influence the risk of infection.

The available literature assessing outcomes following TJA in patients with previous fractures and/or hardware is conflicting. However, given some reports in the literature, it can be inferred that a history of extensive surgery in the joint and/or retained hardware increases the complexity of a subsequent TJA and compromises the outcome, including the possibility for higher incidences of subsequent SSI/PJI.

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QUESTION 2: In patients with prior septic arthritis, what strategies should be undertaken to minimize the risk of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Prior to elective arthroplasty, infection in the joint with prior septic arthritis needs to be ruled out using appropriate diagnostic tests. In the presence of an active infection, two-stage joint arthroplasty is recommended.

Single-stage joint arthroplasty may be considered when all diagnostic tests are normal and there is no active soft tissue involvement (such as a sinus tract or abscess).

Single-stage arthroplasty is a reasonable treatment strategy in patients with septic arthritis caused by Mycobacterium tuberculosis (TB), where anti-tuberculous medications have been commenced and in the absence of a sinus tract or extensive soft tissue involvement.

Antibiotics (no more than 5% by weight), targeted towards the prior organism, if known, should be added to cement during arthroplasty.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 88%, Disagree: 7%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Systemic or active infection is an absolute contraindication to arthroplasty when an infected joint is the source of sepsis [1]. It is important to identify if a patient has an active or quiescent infection in the joint [2]. Some inflammatory serum markers are commonly measured, such as white blood cells, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) in the evaluation of patients with septic arthritis [3]. Furthermore, joints should be considered for aspiration when patients have elevated serum inflammatory markers. A high white cell count is specific for diagnosing septic arthritis, but sensitivity is low, especially using the cutoff value of 50.0x 10^3/μL, which is the most commonly published value [4]. Bone biopsy may be of diagnostic value, in light of evidence of a quiescent intracellular *Staphylococcus aureus* [5].

Joint arthroplasty for septic arthritis has long been considered a high-risk procedure [6]. Pre-existing osteomyelitis is suggested to be more important than septic arthritis [7]. No high-quality rand-

omized trials have assessed the effectivenesses of different treatment strategies. The majority of the published literature are case series without controls. Treatment strategies are based largely on opinion and experience with infected arthroplasties. However, the reported experience of the majority of reporting groups is similar.

Staged hip arthroplasty has been performed successfully in acute septic arthritis [8]. In one case series of 18 patients, 11 underwent two-stage hip arthroplasty, and 7 underwent single-stage hip arthroplasty. There was no recurrence of infection at a mean of 70 months follow-up [2]. In a series of 53 hip and knee arthroplasties, Bauer et al. compared acute septic arthritis treated with two-stage joint arthroplasty and quiescent "cured" septic arthritis treated with single-stage joint arthroplasty. They reported a cure rate of 87% with two-stage joint arthroplasty in active septic arthritis and 95% survivorship with single-stage surgery in cured septic arthritis. They did not identify any additional risk factors for recurrence of infection [9]. However, a further case series from 2008 reported a reinfection rate of 14% with a total complication rate of 36% [10].

Huang et al. described their case series of 14 patients with septic arthritis of the hip treated with a two-stage revision. The mean interval between stages was 12 weeks. The second stage procedure was performed with cementless implants. There were no recurrences at a mean of 42 months [8]. Romano et al. used a preformed spacer in a two-stage strategy with a mean interval of 22 weeks before implantation of cementless implants. They report a 95% survivorship with one failure due to infection at a mean follow-up of 56 months [11]. A Korean group reported on a series of nine patients at a mean follow-up of 42 months. One patient required a repeat first stage and another patient developed infection after the second stage [12].

Lee et al. reported on a series of 20 consecutive knee arthroplasties performed in patients who had a history of quiescent septic arthritis. They identified one postoperative infection at 3.5 years and recommended a single-stage revision after a judicious infection workup [13]. Nazarian et al. proposed a two-stage strategy for septic knee arthritis following their studying examining 14 patients which resulted in complete eradication of infection at a mean follow-up of 4.5 years. The interval between stages was three months [14].

The use of a spacer has been advocated as a temporizing measure due to its ability to elute antibiotics, but also to improve function between stages [15,16]. Fleck et al. reported on 14 patients who underwent two-stage hip arthroplasty, though four patients did not undergo the second stage with two reporting good function from their spacer [17].

Single-stage hip arthroplasty has been promoted for quiescent or cured infection. One series of 19 hips reported good function with no recurrence of infection using this technique. The authors recommended a thorough infection workup to ensure no evidence of active infection [18].

Two-stage joint arthroplasty has been advocated by some case series, though not randomized controlled trials [19]. In TB infection, single-stage arthroplasty appears to be a safe option [18]. However, the authors recommend prolonged anti-tuberculous medications. A series of Charnley hips from 2001 with the longest follow-up at 28 years found that 5 recurrences occurred out of 60 patients, with the failure of the acetabular component being the most common cause for revision [20]. There is a risk of postoperative infection in those patients with the untreated disease or those on corticosteroids [21]. Where sinus tracts exist, or extensive bony destruction with multiple abscesses predominate, a two-stage strategy may be recommended [22,23].

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QUESTION 3: Does the presence of prior projectile missile/bullet fragments in a joint predispose the patient to a higher risk of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)? If so, what should be done to reduce the risk of SSI/PJI?

RECOMMENDATION: The presence of a prior projectile missile/bullet fragments in a joint, unless the joint was previously infected, does not increase the risk of subsequent SSI/PJI in patients undergoing elective arthroplasty in the same joint.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 71%, Disagree: 18%, Abstain: 11% (Super Majority, Strong Consensus)

RATIONALE

The literature regarding this injury gives few guidelines regarding the appropriate patient evaluation and subsequent risk of SSI/PJI if total joint arthroplasty (TJA) is ultimately indicated. Typically, individuals with projectile missile/bullet fragments with possible intraarticular involvement will undergo an evaluation for a traumatic arthrotomy, which may involve a joint aspiration or a saline dye load challenge [1,2]. The presence of retained ballistic fragments within the intraarticular space can cause mechanical and destructive changes due to third-body wear or the initial damage to the articular surface from trauma. The lead components of bullet fragments are soluble in synovial fluid [8] which can lead to a proliferative synovitis and destructive arthritis, which in numerous cases has led to lead arthropathy and plubism (lead poisoning) [2–9]. The concept of "autosterilization" of bullets creating an antiseptic wound has been disproven [10,11]. Tornetta et al. demonstrated that five of seven patients with low velocity intraarticular gunshot wounds without radiographic injury contained intraarticular debris (skin, clothing, bullet fragments) [12]. Therefore, the concern for secondary infection leading to septic arthritis due to retained fragments and foreign body exists [13]. However, there are a limited number of studies available describing the risk for subsequent SSI/PJI following a projectile missile/bullet injury to a lower extremity joint indicated for a TJA.

Although intraarticular gunshot wounds are uncommon, it is recommended that these injuries be managed with irrigation and debridement to prevent subsequent articular injury [1,2,14]. Accompanying fractures should undergo open reduction and internal fixation in an attempt to preserve the joint [1,2]. In small cohort, elective TJA may be indicated due to post-traumatic arthritis, chronic pain and nonunion. In a small retrospective series by Naziri et al. [15], four patients presenting with gunshot wounds to the hip, subsequently underwent elective total hip arthroplasty (THA) following their injury. All patients achieved excellent clinical and radiographic outcomes with no incidence of infection at a mean follow-up of 26 months (range 12 to 24 months). A separate study by Herry et al. [16] assessed clinical outcomes following total knee arthroplasty (TKA) in two patients who had severe ballistic injuries requiring sequential complex surgeries (e.g., management of bone defects, hinged prostheses and muscle flap). Due to their extensive bone and soft tissue injuries, both patients required revision TKA secondary to PJI. Haspl et al. [17] reported on 10 arthroplasties performed at a mean of 24 months (range 9 to 42 months) after gunshot injuries or blast injuries with retained missile fragments in the hip, knee and shoulder. Two knee arthroplasty patients were identified as having PJI where the infecting organism was *Staphylococcus aureus* at 22 and 23 months after their arthroplasty procedure. Following unsuccessful management of their infection, both patients went on to a successful arthrodesis.

There is a paucity of literature describing outcomes following projectile missile/bullet injury and the risk for SSI/PJI following TJA. Additionally, due to the nature of the studies (e.g., case series), small numbers and heterogeneous patient populations, it is difficult to independently assess the impact of projectile missiles/bullets on TJA outcomes. The clinical presentation of a destructive arthritis due to third body wear, proliferative synovitis or from the initial trauma can present similarly to an indolent infection/septic arthritis. Therefore, evaluation for presence of infection may be warranted preoperatively. Also, it can be inferred that the degree of soft-tissue injury as reported by the Gustilo Classification, Mangled Extremity Severity Score (MESS) and limb salvage index (LSI), may help identify TJA candidates at greatest risk for SSI/PJI.

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1.4. PREVENTION: HOST RISK MITIGATION, GENERAL FACTORS

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QUESTION 1: Can immunotherapy and immunoprophylaxis be used to prevent biofilm formation and implant-associated infections?

RECOMMENDATION: Yes. Although no vaccine or passive immunization has been approved by the Food and Drug Administration (FDA) for an orthopaedic indication, a four-antigen vaccine (SA4Ag) with established safety and immunogenicity in healthy volunteers is currently being tested for efficacy in a phase II clinical trial of spine fusion patients. This is also supported by evidence from the literature regarding cochlear implants for children showing a decreased incidence of pneumococcal meningitis. However, there are no high-level studies supporting this trend with evidence and further study needed.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 62%, Disagree: 18%, Abstain: 20% (Super Majority, Weak Consensus)

RATIONALE

It has been well-established that foreign body implants are a nidus for infection by biofilm-forming bacteria [1–3]. Thus, increasing host immunity against the most common pathogens associated with a particular implantation procedure is a rational approach to reduce postoperative infections [4,5]. Additionally, immunotherapy and immunoprophylaxis have been used in various surgical disciplines to prevent surgical site infections (SSI) with varying success rates [6,7]. This has also been evaluated in orthopaedics, primarily with vaccines and passive immunizations against *Staphylococcus aureus*, as this is the most prevalent bacteria associated with these infections [8]. Various *S. aureus* antigens have been incorporated into vaccines with varying levels of success [9,10]. A few investigators have also investigated antigen vaccines against *Staphylococcus epidermidis* [11,12].

To identify the clinical and basic science evidence to support this intervention, a systematic review was completed on the peer-reviewed literature identified by a PubMed search performed on February 8, 2018 using the key words "immunoprophylaxis or immunotherapy or vaccine or vaccination + implant + infection or biofilm." This literature search identified 136 references from 1974 to 2018. After eliminating 56 that did not contain information directly addressing the question, the remaining 80 were divided into three categories: Primary Clinical Research (n = 5, four positive, one negative), Primary Pre-clinical Research (n = 47, all positive), and Reviews (n = 27, 25 positive, two negative).

In the specific case of cochlear implants for children, vaccination with seven-valent pneumococcal conjugate vaccine (PCV7) (Prevnar®), 23-valent pneumococcal polysaccharide vaccine (PPV23) (Pneumovax®) or both, according to the Advisory Committee on Immunization Practices (ACIP) schedules for persons at high risk, immunoprophylaxis has been indicated to reduce the incidence of pneumococcal meningitis, primarily from *Streptococcus pneumoniae* implant-associated infections. As summarized in a systematic review by Wei et al. [13], scientific data supports the FDA recommendation of pneumococcal vaccination for the prevention of meningitis in cochlear implant recipients. While randomized control trials have not been performed to formally establish immunoprophylaxis efficacy, the incidence of pneumococcal meningitis in children receiving cochlear implants has been reduced from that of the pre-vaccine era. Importantly, this conclusion is also supported by strong pre-clinical data demonstrating that the PPV23 vaccine protects rats from implant-associated infections following *S. pneumoniae* challenge via hematogenous and middle-ear routes [14].

A review of the pre-clinical literature revealed 14 primary research articles that demonstrated the efficacy of immunotherapy and immunoprophylaxis to prevent biofilm formation and implant-associated infections. The pathogens studied were *S. aureus* [9,15–21], *Streptococcus epidermidis* [11,12], *Enterococcus faecalis* [21,22], *Aggregatibacter actinomycetemcomitans* [23], and *S. pneumoniae* [14]. However, translating this research to human subjects remains a challenge as evidenced by the results of several anti-*S. aureus* vaccines and passive immunizations that have been investigated in clinical trials [6,24]. Tefibazumab was shown to be safe in phase II trials against *S. aureus* bacteremia [25], but its efficacy is yet to be proven. Veronate, an intravenous immune globulin, failed to prevent staphylococcal sepsis in infants [26]. A vaccine against *S. aureus* IsdB failed to prevent sepsis in cardiothoracic patients and was associated with increased mortality [27]. A vaccine against types 5 and 8 capsular polysaccharides failed to show any efficacy in preventing infection in end-stage renal disease patients undergoing hemodialysis [28]. On the positive side, a vaccine against four *S. aureus* antigens has been shown to be safe and immunogenic in humans in phase I trials [29]. Most recently, another four-antigen vaccine has also demonstrated safety and efficacy beyond one year post-immunization in healthy volunteers [30]. This vaccine is currently being tested for efficacy in spine fusion patients and the study is expected to be completed in late 2018.

Given that (1) the acknowledged efficacy of the FDA-approved pneumococcal vaccines to reduce the incidence of meningitis in

children receiving cochlear implants, (2) the experimental evidence demonstrating plausible mechanisms and in vivo proof of concept with various pathogens and animal models and (3) the ongoing clinical trials based on promising efficacy data, we conclude that immunotherapy and immunoprophylaxis can be used to prevent biofilm formation and implant-associated infections in some situations.

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QUESTION 2: Does routine screening for diabetes and glycemic control reduce the risk of surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: The routine screening for diabetes and glycemic control has the potential to reduce the incidence of SSI and/or PJI following total joint arthroplasty (TJA).

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 96%, Disagree: 3%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

The burden of diabetes is rising, and it is projected that in the next 20 years the number of diabetics in the United States will reach 44 million, about two times the present prevalence [1,2]. Patients with diabetes, especially those with inadequate glycemic control, are at

increased risk for both joint-related and systemic adverse outcomes following TJA [3–6], of which PJI has been the most studied. Multiple professional organizations have published screening recommendations for diabetes [7–10]. While there are slight differences between them, they all agree that patients with an increased risk for diabetes should be screened. It has been found that a large proportion of patients undergoing TJA have undiagnosed diabetes; hence, it is reasonable to provide screening recommendations for this patient population [11].

Diabetes is an established risk factor for severe osteoarthritis [12], and a higher prevalence has been reported in patients undergoing TJA [13,14]. In a recent study, the prevalence of diabetes in patients undergoing TJA was 20.7%, which is almost two times the rate within the general population [15,16]. Interestingly, 40.9% (8.4% of the total cohort) were undiagnosed. Moreover, 38.4% of the total cohort were pre-diabetic, resulting in a total of 59.1% dysglygemic patients. This could explain why numerous studies show that perioperative hyperglycemia, elevated glycated hemoglobin (HbA1c) and high glucose variability are associated with PJI even without a diagnosis of diabetes, as these patients are simply unaware of their dysglycemic status [17–19].

The fact that individuals approaching TJA undergo preadmission testing provides an ideal screening setting, for both patient and physician. Screening TJA patients for diabetes could allow early detection and rapid treatment, which may reduce the burden of diabetes and both its surgical and non-surgical complications. Furthermore, patients with inadequate glycemic control and undiagnosed diabetes may be treated and appropriately optimized in the preoperative setting which could improve their outcomes. Furthermore, lifestyle changes and pharmacologic interventions may reduce progression and delay development in undiagnosed diabetics and pre-diabetics [7,20,21].

Although no studies exist to show that tight glycemic control could reduce the rate of PJI following TJA, it is well-established that inadequately-controlled diabetes is associated with higher rates of PJI. Based on the potential link between strict glycemic control in the perioperative period and reduction in PJI rates, and due to the extremely high rate of unknown diabetics and prediabetics in patients undergoing TJA, we extrapolate that screening all patients prior to surgery could assist in reducing the incidence of SSI and PJI.

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QUESTION 3: What is the most accurate marker for assessing glycemic control that best predicts surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: While there is evidence showing an association between elevated glycated haemoglobin (HbA1c) and fasting blood glucose and increased risk for subsequent SSI/PJI, this association is not strong. Recent findings suggest that fructosamine in the preoperative period and glucose variability in the immediate postoperative period may provide greater prediction of SSI or PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 76%, Disagree: 8%, Abstain: 16% (Super Majority, Strong Consensus)

RATIONALE

Diabetes mellitus (DM) patients are predisposed to a host of complications following total joint arthroplasty (TJA) [1–3], with SSI and PJI being perhaps the most dreaded [4]. Glycemic control throughout the perioperative period has been a focus of many recent studies, since it could serve as a modifiable risk factor and targeting it holds the potential to reduce SSI/PJI rates following TJA [5–9]. However, the proper marker for assessing glycemic control in the perioperative period remains unknown. Studies into the subject have produced conflicting results due to diversity in the marker used for assessment, timing of assessment and different cutoff values used for stratifying patients.

Traditional markers for assessing glycemic control can crudely be divided into long-term (HbA1c) and short-term (glucose levels) in the preoperative and postoperative period. A recent meta-analysis of ten studies suggested that elevated HbA1c levels were not significantly associated with a higher risk of SSI/PJI after TJA (pooled odds ratio (OR): 1.49, 95% confidence interval (CI): 0.94 to 2.37, p = 0.09) However, this was most likely due to the low threshold (7%) chosen to define inadequate control in the majority of the studies, with accumulating evidence to support the utility of preoperative HbA1c levels above 7.5 to 8.0% as a predictor for PJI. Similar to HbA1c, the prognostic value of perioperative hyperglycemia remains unclear [10,11]. Studies supporting the association between perioperative hyperglycemia and PJI were underpowered and did not take into account other confounders [9,12]. In those studies that did include important confounders, the association was markedly attenuated [5–9,12–14].

We conducted a systematic review and found ten studies examining the association between glycemic control and PJI. Of those, six examined HbA1c solely [10,11,15–18], one looked at perioperative control alone [12] and three assessed both [5,6,8]. Similar to the meta-analysis mentioned above, the results of our review suggest that higher HbA1c levels are not clearly associated with higher PJI rates, possibly due to inaccurate cutoffs to define inadequate glycemic control. We also found that hyperglycemia in the perioperative period appears to have some association with PJI; however, this relationship is complex and is not well-characterized by the studies reviewed given their varied design.

The uncertainty of the independent role perioperative HbA1c or hyperglycemia have on PJI raises the question of whether these are the most appropriate markers for assessing glycemic control. The focus on fluctuation of glucose around the mean has gained popularity in recent years and has been studied extensively [19–21]. Both in vivo and in vitro studies attribute the negative effects of these fluctuations to the activation of pro-inflammatory proteins and excessive oxidative stress [22]. Short-term fluctuations in glucose levels may have a larger effect on inflammatory cytokine levels than continuous hyperglycemia that may impair host defense from infection [23,24]. Lately, fructosamine (in the preoperative period) and glucose variability (in the postoperative period), which are medium and short term markers for glycemic control, respectively, were shown to correlate strongly with the risk for PJI in both diabetics and unknown-diabetics who seemed to be adequately-controlled based on traditional markers [25].

Fructosamine measures the level of glycated serum proteins and reflects the average glucose levels over a 14- to 21-day time period [26]. It better detects fluctuation and rapid variations of glucose and may detect short term hyperglycemic events better than HbA1c. In a recent study, fructosamine above 292 mmol/L had a better association with SSI and PJI compared to HbA1c when 7% was used as a threshold for inadequate control. One of the immense advantages of fructosamine, compared to HbA1c, is the shorter half-life of the glycated proteins that may reflect the effect of treatment within a week or 2 as opposed to glycated hemoglobin that could take up to 120 days.

In conclusion, our systematic review of the literature on the subject could not detect the most accurate marker for assessing perioperative glycemic control and further research in this area, with consistent study design, is required to answer this question. Based on recent findings, we conclude that fructosamine can serve as an alternative to HbA1c in the setting of preoperative glycemic assessment. Further research to solidify its utility and specify and exact threshold level indicative of inadequate glycemic control should be conducted. With improvement in technology, non-invasive continuous glucose monitoring devices could become more readily available. Future studies should evaluate the role of continuous glucose monitoring in the perioperative period to reduce glucose variability.

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QUESTION 4: What is the threshold for glycated haemoglobin (HbA1c) that is predictive of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI) in patients undergoing orthopaedic procedures?

RECOMMENDATION: The upper threshold for HbA1c that may be predictive of subsequent SSI/PJI is most likely to be within the range of 7.5 to 8%.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 88%, Disagree: 3%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

A wide range of complications have been reported among patients with diabetes undergoing orthopaedic procedures, namely SSIs. Therefore, it is thought that maintaining appropriate glycemic control during the perioperative period is crucial for potentially decreasing the risk of such complications [1–3]. Serum HbA1c is a surrogate for patient glycemic status over a two- to three-month period and is widely used as a marker for perioperative glycemic control [4].

The American Diabetes Association (ADA) guidelines recommend a maintenance of an HbA1c level of less than 7% for patients with diabetes in order to minimize potential complications [5]. However, the orthopaedic literature is less conclusive regarding a specific threshold that would reduce the risk of complications. Several studies were not able to reach significance between a specific HbA1c threshold and postoperative infection [1,3,6–10], while others reported a significant association between infections and HbA1c level, but with no clear consensus on one predictive value among the studies [2,5,11–21]. It is worth noting that many of these studies adopted the ADA recommended HbA1c value of 7% as a cutoff level in their design phase to stratify their cohorts (diabetic vs. non-diabetic) and attempted to validate this previously-established threshold rather than examining HbA1c as a continuous variable [1,3].

With regards to total joint arthroplasty (TJA), Han et al. found an HbA1c level of more than 8% to be significantly associated with a higher risk of postoperative wound complications for patients undergoing total knee arthroplasty (TKA) [15]. Similarly, Hwang et al. found that a HbA1c greater than 8% is associated with superficial SSIs following TKA in patients with diabetes, while the HbA1c level of 7% was not detected as a significant cutoff value for higher likelihood of infection or wound complications, in contradiction to the guidelines of the ADA [17].

Cancienne et al. found that patients having a HbA1c level equal to or more than 8% were more likely to have an infection within one year of performing TKA compared to those having HbA1c levels less than 8% (adjusted odds ratio (OR): 1.7, 95% confidence interval (CI) 1.2 to 2.4, p = 0.004). However, it was indicated that this threshold of 8% is of limited clinical utility when taken as an independent predictor for postoperative infection due to its poor sensitivity and intermediate specificity [2]. In another parallel study of total hip arthroplasties [14], Cancienne et al. also identified that a perioperative HbA1c of more than 7.5% is a significant risk factor for the development of postoperative PJI, yet, is of poor clinical utility as a stand-alone predictor for PJI [5]. Stryker et al. reported that patients with a preoperative HbA1c level of more than 6.7% have nine times the odds of having increased risk of wound complication following primary TJA compared to those having a HbA1c less than 6.7% (95% CI 1.14 to 71.20, p = 0.03) [19]. Jamsen et al. identified a threshold of HbA1c of 6.5% above which the rates of PJI were significantly higher [18]. On the other hand, a recent study by Tarabichi et al. presented receiver operating characteristic (ROC) curves and used Youden index to estimate the optimal cutoff value of HbA1c predictive of complications to find the threshold of 7.7% to be predictive of PJI in TJA (95% CI 6.25 to 8.05, Youden index 0.38, cutpoint 0.019) [20]. A systematic review and meta-analysis by Yang et al. indicated that the cutoff HbA1c value of 7% as predictive of PJI remains controversial [21]. Similarly, a recently released systematic review and meta-analysis by Shohat et al. indicated that the orthopaedic literature has failed to agree on the optimal HbA1c value predictive of SSI in TJA [22].

Cancienne et al. reported an HbA1c level of 7.5% to be a significant threshold predictive of infection [12] in spinal and cervical surgery. Hikata et al., on the other hand, found that preoperative HbA1c values were significantly higher in patients with diabetes who developed postoperative SSIs and recommended that HbA1c levels should be maintained below 7% to prevent SSIs [16].

In one of the very few studies addressing foot and ankle surgeries and HbA1c threshold, Domek et al. reported a significant association between greater HbA1c values and infections, yet they were not able to identify an HbA1c value that could potentially predict a greater risk of infection [13].

Among the minimal number of studies on arthroscopy, Cancienne et al. recently reported that a perioperative HbA1c of 8% could serve as a threshold, yet they found limited clinical applicability due to low sensitivity [11].

Generally, Dronge et al. reported findings from a cohort of 490 diabetic patients who underwent non-cardiac surgery, of which 63 underwent orthopaedic surgeries, and detected that HbA1c levels less than 7% were associated with a significantly lower risk of postoperative infections [14].

In conclusion, studies on different types of orthopaedic procedures reported a broad range of HbA1c threshold levels that may be predictive of postoperative infections. No consensus was reached, neither within studies addressing the same orthopaedic procedures nor across studies targeting different orthopaedic surgeries. The ultimate HbA1c threshold remains controversial; however, the literature indicates that this threshold is most likely in the range of 7.5 to 8%. Larger studies examining the optimal threshold for HbA1c as well as studies examining alternative markers of glycemic control are necessary [10].

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QUESTION 5: Is thrombocytosis associated with an increased risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing orthopaedic procedures?

RECOMMENDATION: It is unlikely that thrombocytosis is associated with an increased risk of postsurgical SSIs/PJIs. However, patients with severe thrombocytosis should undergo evaluation prior to orthopaedic procedures.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 89%, Disagree: 4%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

The upper limit of the platelet count differs among various sources and laboratories, but is generally accepted to be in the range of 350,000 to 450,000/mL (350 to 450 x 10^9/L) [1,2]. Newly recognized thrombocytosis may be a marker for the presence of a clonal (neoplastic, autonomous) hematologic disorder or a reactive phenomenon (secondary) [1].

Reactive thrombocytosis refers to thrombocytosis in the absence of a chronic hematologic disorder and is due to any inflammatory process such as bacterial infection, neoplasia, sepsis, multiple trauma or a recent surgery. Reactive thrombocytosis associated with underlying inflammation or infection constitutes the vast majority of cases encountered in practice [1-3].

Elevated levels of interleukins (IL) and C-reactive protein (CRP) are associated with infections. Any condition that elevates serum IL levels (especially IL-6) subsequently triggers an increase in circulating platelet count [4,5]. Although the exact mechanism is

unknown, more than 81% of patients with reactive thrombocytosis have elevated serum levels of IL-6 or C-reactive protein [6,7]. Reactive thrombocytosis is usually associated with modest elevations in platelet count (up to 700,000/μL), normal platelet structure and function and a normal bone marrow. However, the concentration of IL-6 in the serum does not predict the observed platelet counts [7].

In reactive thrombocytosis, the structure and function of platelets are believed to remain normal, thus bleeding during or after surgical procedure is thought to be unlikely. In the absence of abnormal bleeding and hematoma formation, the association between thrombocytosis and subsequent SSI/PJI remains undefined. In non-orthopaedic literature, one study utilizing an administrative database suggested a link between thrombocytosis and increased infection in neurosurgical procedures [8]. The latter study, however, suffered from all the issues related to databases and lack of granular data to prove such an association.

Therefore, an association between reactive thrombocytosis and an increased risk for infection remains unproven. However, based on the fact that reactive thrombocytosis could be a sign of an ongoing neoplasm, infection or other important pathologies, the condition should be investigated prior to elective orthopaedic procedures.

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1.5. PREVENTION: RISK MITIGATION, LOCAL FACTORS

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QUESTION 1: Is preoperative methicillin-resistant *S. aureus* (MRSA) decolonization effective at reducing surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing orthopaedic procedures? If so, is preoperative MRSA decolonization cost-effective?

RECOMMENDATION: No definitive recommendation can be made regarding the routine implementation of preoperative S. aureus screening and decolonization protocols due to conflicting literature. Additionally, no definitive recommendation can be made about selective or universal treatment, although the universal treatment strategy seems to be the most cost-effective strategy and easiest to implement. Alternatives to mupirocin such as povidone-iodine nasal ointment may obviate the concern for antibiotic resistance raised by universal treatment protocols.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 86%, Disagree: 7%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

There is evidence in the literature that patients colonized with *Staphylococcus aureus* in their nasal or skin flora are at increased risk of SSIs and PJIs after total joint arthroplasty (TJA) [1–3]. SSIs resulting from *S. aureus* are significantly higher among TJA patients compared to other orthopaedic surgeries [4]. It is not clear whether this increased risk is exclusively due to the carrier state or the association of *S. aureus* colonization with other medical risk factors for PJI such as diabetes, obesity, renal insufficiency, inflammatory arthritis or immunosuppression [2,5,6]. For example, Maoz et al. [7] analyzed data from 3,672 primary and 406 revision hip arthroplasties and found that *S. aureus* colonization was associated with higher PJI rates but was not an independent risk factor in a multivariate analysis.

That said, the existence of an endogenous contamination pathway has long been recognized among PJI cases [8]. While the concordance between wound and nasal isolates among carriers is high, *S. aureus* infections can also be found in non-carriers [2,9,10]. The actual preponderance of the endogenous route over the traditional exogenous mode of infection acquisition is not constant and may be based on geography and institution, depending on the epidemiological setting. It has been shown that institution-wide MRSA endemics do not necessarily lead to a high MRSA infection risk after elective hip and knee arthroplasty [11]. However, many institutions have attempted to minimize this potentially modifiable source of contamination by instituting preoperative screening and decolonization protocols in *S. aureus* carriers to reduce infection rates.

Several different approaches have been described. A perfect screening test has a high sensitivity to identify all *S. aureus* carriers at a reduced cost, and a perfect treatment regimen would be easy to administer and cost-effective, while achieving preoperative *S. aureus* eradication without short- or long-term or patient- or population-based adverse effects. Standard culture techniques are often used, but their sensitivity is highly variable depending on the number of samples taken for each patient and the method of sampling. Naturally, screening multiple body sites is more sensitive for identifying carriers and using nasal swabs as a surrogate for colonization testing may only identify two-thirds of true MRSA carriers [12,13]. Molecular

polymerase chain reaction (PCR) based screening techniques may provide results in a shorter time frame, but this technique is more expensive, and there is conflicting evidence regarding the theoretical advantage of PCR over traditional cultures [14,15].

Treatment of *S. aureus* carriers has traditionally been achieved utilizing nasal mupirocin ointment twice a day with whole-body chlorhexidine once a day for the five days preceding surgery [16,17]. The biggest criticism of this treatment regimen is that increased use of mupirocin, an antibiotic, can potentially increase the risk for antibiotic resistance.

Other decolonization alternatives use antiseptics, such as povidone-iodine, rather than antibiotics (i.e., mupirocin) to achieve *S. aureus* eradication. It is relevant to acknowledge that not all povidone-iodine products are equally effective in eliminating nasal *S. aureus* [18]. A specific povidone-iodine product for nasal use that contains excipients which protect the solution against deactivation by nasal secretions was developed and tested favorably in vitro against traditional products such as mupirocin [19]. This povidone-iodine treatment rapidly achieves a significant reduction in bacterial counts after one hour of treatment, and a prospective, open-label, randomized clinical trial demonstrated that preoperative decolonization resulted in significantly fewer *S. aureus* infections compared to five days of mupirocin for patients undergoing primary or revision TJA or spinal fusion [19,20].

These treatment regimens are effective for reducing *S. aureus* colonization in patients, but *S. aureus* colonization persists in approximately 20% of patients despite adequate treatment [3,21–24]. There is also a lack of long-term decolonization even after successful preoperative eradication [25,26]. The risk of infection after decolonization, especially among MRSA carriers, is not lowered to baseline of a non-colonized patient [2,21,24,27–29]. Nevertheless, there is moderate evidence derived from several retrospective studies suggesting that either universal preoperative treatment or universal screening and treatment of identified carriers may be beneficial for reducing overall SSIs [24,30–32] and specifically for *S. aureus* and MRSA after elective orthopaedic surgery [24,33–36].

The cost-effectiveness of *S. aureus* screening/treatment is derived from the cost savings of preventing infections by implementing a screening and decolonization protocol [37]. Therefore, adopting a universal decolonization procedure rather than a screen-and-treat protocol seems to be the most cost-effective approach for treating *S. aureus* colonization based on the prevalence of *S. aureus* carriage, the costs of screening and treatment, and the rate of PJIs and socio-economic costs of dealing with PJI. It is also easier and less resource-consuming to implement a universal decolonization, and, more importantly, no carrier would be left untreated due to screening sensitivity issues or timely identification. However, the treat-all approach is associated with theoretical costs that are often not considered in economic models such as the risk of emerging resistance to topical antimicrobials like mupirocin [38]. Although universal decolonization seems to be the most cost-effective, one or two-swab screen-and-treat strategies also offer cost-effective results. Ultimately, choosing the most appropriate strategy may depend on the baseline PJI risk at each institution and patient subpopulations. In this regard, it is important to stress that although specific medical and demographic risk factors for *S. aureus* (and MRSA) colonization in total joint arthroplasty candidates can be found, there is a large proportion of carriers with no known risk factor(s). Thus, selective screening of high-risk population subgroups is not an effective approach to accurately identify carriers [5,6,27,39,40]. Definitive evidence evaluating the real value of preoperative *S. aureus* decolonization at reducing PJI after total joint arthroplasty is still lacking, as the evidence demonstrates conflicting reports.

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QUESTION 2: What methods for methicillin-resistant/methicillin-susceptible *S. aureus* (MRSA/MSSA) decolonization exist? What are the benefits and risks associated with the use of each?

RECOMMENDATION: Methods of nasal decolonization include 2% mupirocin ointment, 5% povidone-iodine solution, alcohol-based products and chlorhexidine-based products. Each method has its own advantages and disadvantages related to proven effectiveness, potential for emergence of bacterial resistance and patient compliance. However, no consensus has been reached on the preferred method for decolonization for MRSA, with all products having a potential role.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 3%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

One of the most common organisms responsible for periprosthetic joint infection (PJI) of the hip and knee is MSSA and MRSA. Patients colonized with these organisms have an increased risk of PJI [1–6]. Up to 20 to 30% of the general population are asymptomatic carriers of MSSA and the nares are the main site of colonization [5,7]. Nasal decolonization of such patients to reduce bioburden with MRSA/MSSA has been shown to reduce the rate of PJI but the evidence is limited by underpowered studies [3] or clouded by additional treatment measures in colonized patients [7–17]. Often, decolonization is combined with other prevention measures such as bathing/showering with antiseptic or the use of perioperative vancomycin [1,3,15–18]. Thus, many governing bodies providing recommendations for the prevention of PJI have difficulty agreeing on the best method for decolonization and whether it should be routinely performed [19]. Currently, there are several available options for nasal decolonization, each with its own advantages and disadvantages.

Mupirocin, applied to the nares twice daily for five days preoperatively, has been the most commonly used nasal decolonization strategy for MRSA/MSSA. The medication targets most species of *Staphylococcus* in a safe and reliable manner [20]. The advantage of mupirocin is its low-cost and proven efficacy for decolonization and reduction of PJI based on multiple studies [4,10,13–15]. It leads to a rate of decolonization of 94% at one week and 65% at two weeks [21]. The disadvantage of this agent is the potential for emergence of resistant organisms which has been shown to occur in 3.3% of cases [22], with prior use of the agent increasing the rate of resistance ninefold [23]. The other disadvantage of the agent is patient non-compliance as application of the ointment to nares twice a day for five days is demanding [24].

Povidone-iodine, applied to the nares as a 5% solution one hour before surgery, has been utilized in an effort to increase patient compliance and to mitigate bacterial resistance. Unlike mupirocin, which is bactericidal and relatively long acting, povidone-iodine provides bacterial suppression for up to 12 hours after application. While this agent has been less intensively studied than mupirocin, it has been shown in some studies to have similar results in terms of reduction of PJIs [25].

Some newer agents have been introduced recently, namely alcohol-based and chlorhexidine-based solutions, that aim to increase patient compliance and combat emergence of resistance [26]. Nozin is a non-prescription ethyl alcohol-based nasal sanitizer. Such products show promise as an alternative to antibiotic-based treatments [25] with the advantages of preventing antibiotic resistance and administration in a single application [19].

However, larger, well-designed studies will be required to demonstrate that routine screening and decolonization are cost-effective and to determine the optimal method for decolonization. Because of the low prevalence of PJI, any study designed to demonstrate a significant decrease in infection rate must necessarily include a large number of patients. For instance, to demonstrate a significant decrease from 4 to 2%, one would need to include more than 1,100 patients in each group (treated and non-treated), as stated by Sousa et al. [3]. Also, current trials report very limited data on other outcomes such as adverse effects, detection of antibiotic resistance and cost-effectiveness of the various decolonization methods [1,3,15,27,28].

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QUESTION 3: After a patient undergoes methicillin-resistant *Staphylococcus aureus* (MRSA) decolonization, is there a need to re-screen the patient?

RECOMMENDATION: We recognize that a subset of MRSA carriers remains colonized despite preoperative decolonization protocols. Currently, there is no evidence to suggest that re-screening and subsequent repeated MRSA decolonization can change the perioperative prophylactic antibiotic regimen and reduce the risk of periprosthetic joint infection (PJI) further.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 87%, Disagree: 8%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Colonization with both methicillin-sensitive *Staphylococcus aureus* (MSSA) and MRSA increases the risk of staphylococcal surgical site infections after elective hip and knee arthroplasty [1,2]. In the United States, an estimated 0.6 to 6% of the population are nasal carriers of MRSA [1,3]. For identified carriers of MRSA undergoing hip and knee arthroplasty, standard practice includes decolonization prior to surgery followed by perioperative vancomycin for MRSA coverage.

Previous studies have proven that a protocol of screening and decolonization of MRSA among total joint arthroplasty (TJA) candidates is highly successful in reducing the percentage of MRSA carriers [1,4–8]. However, controversy continues with regard to the ability of *S. aureus* decolonization protocols to reduce the prevalence of surgical site infections (SSIs) and PJIs in patients undergoing total hip or knee arthroplasty. In a meta-analysis of four studies [9], the use of a prophylaxis protocol for MRSA decolonization reduced SSI cases by approximately 39%. Another meta-analysis of 19 studies [10] suggested a decrease in the rates of SSI with decolonization. However, five of the included studies did not reach significance and were underpowered. Baratz et al. [11] retrospectively described 3,434 patients who underwent elective primary and revision hip and knee arthroplasty over a two year period. Despite successfully obtaining a 78% MRSA decolonization rate at the day of surgery, the incidence of SSI was not decreased compared to an historical control group.

Several studies have re-screened patients on the day of surgery and identified persistent MRSA carriage in as many as 20% of patients, despite preoperative decolonization protocols [8,11,12]. Similarly, MRSA carriers that have been decolonized and later re-screened for future procedures have shown recolonization rates as high as 38% [13,14]. However, no studies have specifically investigated whether persistent MRSA carriage is associated with an increased risk for SSI compared to previous MRSA carriers who remain decolonized. Furthermore, the cost-effectiveness of re-screening and repeated decolonization of MRSA is another important issue to be considered. Slover et al. estimated that the cost of a revision total hip or knee arthroplasty secondary to infection to be $70,000 [15]. The authors then estimated that a screening and decolonization program needed to result in a 35% reduction in revision rates to be cost-effective [15]. More importantly, extended mupirocin use has been shown to increase the risk of mupirocin resistance in MRSA carriers [16].

An important question is whether re-screening a previously identified MRSA carrier will change the clinical management during current and future elective orthopaedic procedures. For nearly all patients with any history of MRSA colonization, the perioperative antibiotic regimen will include vancomycin, regardless of their most recent colonization status. For certain hospital policies, identifying persistent MRSA colonization on the day of surgery may prompt inpatient contact precautions, while those who have been successfully decolonized may not require contact precautions. It is unknown what effect, if any, these perioperative protocols have on rates of surgical site infections.

The cohort most likely to benefit from re-screening are MSSA carriers and previously non-colonized patients after a certain period of time from the initial screening [12,14]. Studies have shown that re-screening can identify new cases of MRSA [12,14]. Re-screening before an additional surgery may be beneficial for these cohorts, as it may identify new MRSA carriage and prompt a change in perioperative antibiotic selection.

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1.6. PREVENTION: RISK MITIGATION, GENERAL FACTORS

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QUESTION 1: Does prior surgical site infection/periprosthetic joint infection (SSI/PJI) of a joint increase the risk of subsequent infection in another joint? If so, should elective arthroplasty of the joint be withheld in patients with active or treated PJI of another joint?

RECOMMENDATION: Yes. Prior SSI and PJI of a joint increases the risk of subsequent infection in another joint. Elective arthroplasty of the other joint should be withheld in patients with active infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 95%, Disagree: 4%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Active local or systemic infections, as well as prior or current SSI and PJI of a different joint, have all been found to be associated with risk factors for developing PJI in a subsequent joint. [1–8] PJIs have been found to occur in up to 20% of patients with multiple joints in place, with one having an infection [9]. Hematogenous seeding has been thought to play an important role in this process as well as other risk factors present on the first infection.

Murray et al. [10] estimated the risk of hematogenous spread from one joint to another to be as high as 18%. Zimmerli et al. [8] identified that *Staphylococcus aureus* bacteremia increased this to up 29%. In his study, 31 patients (45 prosthetic joints) had *S. aureus* bacteremia with 13 presenting with an infected prosthetic joint. Bacterial sources were seen to be skin and soft tissue, catheters, vertebral osteomyelitis, pneumonia and contralateral prosthetic joints. Furthermore, the risk for hematogenous seeding depends also upon the patient's condition before the infectious event. The origin of the suspected remote infection plays an important role, i.e., skin infections in the lower extremities, often spread the infection by the lymphatic route rather than hematogenous. [7,11] A second study by Swan et al. [12] identified certain events, in patients with multiple comorbidities, that put them at a higher risk of suffering a PJI from a distant location, with most prevalent being recent cellulitis.

Patients having been treated for a prior PJI, have an 11% greater risk of developing a PJI in a new joint. In a study by Bedair et al. [13], the authors specifically addressed patients undergoing total joint arthroplasty after a successfully treated PJI in a previous joint. This multicenter, retrospective, case-control study included 90 patients (35 total hip arthroplasties and 55 total knee arthroplasties). They found that patients who had a history of a treated periprosthetic joint infection had a greater risk of developing a PJI in a subsequent joint (10 of 90 versus 0 of 90 in the control group) (relative risk: 21.00, $p = 0.035$). No other factors were identified to be associated risk factors for developing a second joint infection.

Abblitt et al. [14] also reviewed patients with periprosthetic joint infection and multiple prosthetic joints. A total of 167 patients were identified, out of which 76 had multiple prosthetic joints in situ. Ten patients (13%) developed a PJI in a second location and the rate of infection spreading from one joint to another was 8.3%. This was a retrospective study that reviewed infections in existing arthroplasties and did not include arthroplasties done following an existing PJI.

The data reviewed suggests that in cases of remote infections, the risk of hematogenous seeding exists. This depends also on the pathogen, being higher with infections secondary to *S. aureus*. Therefore, in the scenario of a potential or suspicion of a distant infection, the patient should be delayed for elective arthroplasty surgery until all possible sources of infection are treated. The hazard of getting a new prosthetic joint infected after a PJI at another anatomic site seems to be evident; however, the exact risk is unknown. Patient-related risk factors play a crucial role in the development of PJIs and need to be considered.

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QUESTION 2: What immune system-enhancing strategies can be employed to reduce the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: Besides medical optimization of patients to enhance their immunity, there is some evidence demonstrating that immunonutrients (amino acids), vitamin D supplementation and passive/active immunization against *Staphylococcus aureus* may enhance immune system function, and potentially reduce the incidence of SSIs/PJIs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 74%, Disagree: 11%, Abstain: 15% (Super Majority, Strong Consensus)

RATIONALE

There is a close relationship between immunity and SSIs and PJIs. Thus, the strengthening of the immune system may reduce SSIs and PJIs. The strongest rationale for immune system enhancing strategies to reduce the risk of SSIs and PJIs is that perioperative immunosuppressive therapy is believed to increase these complications. This thinking has led to empirical bundles that include stopping immunosuppressive drugs (i.e., glucocorticoids, disease-modifying antirheumatic drugs (DMARDs) and biologic agents) before elective surgery [1]. Other investigators have concluded that while there is evidence to support the use of methotrexate perioperatively in rheumatoid arthritis patients, it remains unclear whether using anti-tumor necrosis factor (anti-TNF) medications perioperatively increases the risk of SSI [2].

Although cessation of immunosuppressive therapy prior to elective surgery has been adopted as a standard of care for the aforementioned reasons [3,4], there are no data from randomized, double-blind controlled clinical trials available to guide immunosuppressive therapy in the perioperative setting [5]. Thus, to identify the available information on this subject, a systematic review was completed on the peer-reviewed literature identified by a PubMed search performed on February 24, 2018 using the keywords "immunosuppression" or "immunostimulatory," and "SSI" or "PJI" or "elective surgery." This literature search identified 60 references from 1992 to 2018. After eliminating 49 that did not contain information directly addressing the question, the remaining 11 were divided into two categories: Primary Clinical Research (n = 7, four studies were positive [6–9] and three studies were negative [10–12]) and Clinical Reviews (n = 4, all reviews were positive [1,2,5,13]). Of note, a review of the pre-clinical literature failed to identify any research aimed at answering this question.

Activation of the immune system by active and passive immunization is a method that has been applied for many years to cope with many infective organisms. Recently, promising studies have been conducted on active and passive immunization for *Staphylococcus aureus,* which is the main causative agent identified for PJIs [14,15]. Although a vaccine for *S. aureus* has not been introduced clinically, a clinical trial by Pfizer is underway at the moment evaluating the effect of a tetravalent vaccine on patients undergoing spine surgery. There is also the potential for the development of a vaccine against *Pseudomonas* [16,17].

The relationship between immunity and nutrients has long been studied in patients with a poor immune system. The use of glutamine, arginine, omega-3 polyunsaturated fatty acids and ribonucleic acids in the perioperative period has been reported to reduce postoperative complications [18]. In a meta-analysis conducted by Zheng et al., 13 randomized controlled trials including 1,269 patients were evaluated. The meta-analysis revealed that the addition of immunonutrients to routine preoperative diets reduced subsequent SSIs and shortened the hospital stays [19]. Moreover, immunomodulator effects of Eicosapentaenoic acid (EPA) have been elucidated [19]. In a prospective study by Horie et al., administration of preoperative arginine-enriched nutrition reduced superficial, deep and organ-space infection in a cohort of patients undergoing colorectal cancer surgery [20]. On the other hand, one study found that preoperative or perioperative immunonutrition did not reduce the postoperative infectious complications and SSIs in head and neck cancer patients [10].

Vitamin D is an important immune system enhancer, playing an essential role in neutrophil motility, activation of macrophages and inducing T-helper type 1 cells, which target bacterial pathogens that are commonly responsible for PJIs [21,22]. A recent study by Traven at al. demonstrated that low-serum vitamin D levels (25-OH) in patients undergoing joint arthroplasty were associated with an increased risk of 90-day complications as well as PJIs [23]. However, to date, no studies exist to demonstrate that correction of vitamin D deficiency repudiates the reported association. In addition, it is not known what dose and duration of vitamin D supplement are required to correct the deficiency.

Vitamin E also plays an important role in enhancing immune system function via its antioxidant properties. It also reduces apoptosis and increases macrophage activation. Chen et al. demonstrated that murine macrophages with vitamin E-enriched ultra-high molecular weight polyethylene (VE-UHMWPE) particles induced less apoptosis and Tumor Necrosis Factor (TNF) release versus particles without vitamin E [24]. Banche et al. demonstrated that VE-UHMWPE provides a less adhesive surface to *S. aureus* and *E. coli* [25]. On the other hand, Williams et al. reported that the addition of vitamin E to UHMWPE might not reduce clinically relevant rates of biofilm-related PJIs [26]. Further studies are required to better delineate the role of vitamin E in preventing PJIs.

The relationship between smoking and immunity has been established [27]. Smoking, in particular, causes immunosuppression by inactivating macrophages, neutrophils, natural killer cells and lymphocytes [27]. Moreover, smoking causes tissue hypoxia and slows blood flow to tissues potentially preventing the immune cells to reach infecting organisms in a given tissue. Smoking cessation is likely to restore immune function and potentially minimize the risk of subsequent SSIs/PJIs [28].

Greenky et al. have shown that patients with preoperative anemia (hemoglobin level less than 13 g/dL in men and 12 g/dL in women) are at greater risk of PJIs (4.3% in anemic patients compared with 2% in non-anemic patients) [29]. The association between

anemia and a higher rate of SSI/PJI may be explained by numerous factors. Patients with anemia are more likely to have tissue hypoxia, which adversely affects wound healing. Patients with anemia may suffer chronic conditions such as renal disease that in their own right may be associated with SSIs/PJIs. Patients with anemia may be subjected to a higher rate of allogeneic blood transfusion with its immunomodulating effects.

Another cause of immunosuppression is malnutrition. Bohl et al. reported that patients with hypoalbuminemia are at a greater risk of developing PJIs following joint arthroplasty [30]. Malnutrition can be defined as a serum albumin level < 3 .5 g/dL, serum transferrin levels < 200 mg/dL, serum prealbumin < 15 gm/dL, and total lymphocyte count (TLC) < 1,500 cells/mm3 [31]. Dialysis therapy due to renal insufficiency, chronic hepatic insufficiency, malnutrition and depression-psychosis may cause hypoalbuminemia [32]. We should state that the current definitions of malnutrition mostly concentrate on protein deficiency, and the importance of other nutritional parameters such as vitamins, minerals, etc. are not well-studied.

This literature review also found evidence of nonspecific global health treatments that have been described as being immune system enhancing to reduce SSIs/PJIs. These include maintaining body temperature, high concentration of oxygen [13], perioperative glucose control [9] and eliminating blood transfusions [6].

With the available evidence, it is reasonable to propose that discontinuation of immunosuppressive agents, medical optimization of patients with chronic conditions, such as anemia and diabetes, and administration of immunonutrients, such as amino acids and vitamins, are likely to lead to better outcomes after surgical procedures in general and a reduced rate of SSIs and PJIs in particular. Future studies will reveal if vaccines against organisms such as *Staphylococcus aureus* are effective in reducing the incidence of SSIs/PJIs after orthopaedic and other surgical procedures.

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QUESTION 3: For patients awaiting organ transplant who need elective arthroplasty, should the arthroplasty be done before or after the organ transplant?

RECOMMENDATION: We recommend performing arthroplasty after solid organ transplant, using normal antibiotic prophylaxis. Recent studies utilizing publicly available databases compare patients undergoing total joint arthroplasty (TJA) during organ replacement therapy (i.e., hemodialysis) versus after organ transplantation (i.e., kidney transplant) and consistently report less infections in the post-transplant cohort.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 2%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

As the number of primary and revision total joint arthroplasties are expected to increase dramatically, so too will surgical site infections (SSIs) and periprosthetic joint infections (PJIs) [1,2]. Infection is one of the leading causes of failure for primary and revision total knee arthroplasty (TKA) and total hip arthroplasty (THA) [3–5], making patient health optimization and infection prevention paramount.

Furthermore, the elderly population in western countries continues to grow, and mean life expectancy is increasing as is activity level [3]. This is possibly secondary to advances in medical care and the treatment and prevention of chronic medical conditions. As patients continue to live longer with chronic medical conditions, there has been a parallel increase in need for solid organ transplantation (SOT) for end-stage organ failure. And as SOT patients survival improves, the number of these patients undergoing THAs and TKAs is increasing. In 2015, up to 126,670 organs were transplanted globally, including 84,347 kidneys, 27,759 livers, 7,023 hearts, 5,046 lungs, 2,299 pancreases and 196 small bowels [6].

Like the general population, the life expectancy of organ recipients is also increasing, predisposing them to osteoarthritis because of advancing age and ensuing osteonecrosis from corticosteroid and anti-rejection drug administration [7–9]. Previous studies have demonstrated that both end-stage organ failure and SOT patients have good pain relief and function after hip and knee arthroplasty [10,11]. While no level I or level II studies currently exist, the timing of arthroplasty in these patients has been investigated in retrospective and database studies.

Overall, five studies were identified that compared patients receiving arthroplasties during organ arthroplasty therapy to those receiving it after SOT [12–16]. All of the studies were retrospective and investigated end-stage renal disease versus kidney transplantation. Garcia-Ramiro et al. identified a 20% infection rate (2/10) in hemodialysis (HD) patients compared to 50% (4/8) renal transplant patients [13]. In a multicenter study, Lieberman et al. found an 18.7% infection rate in HD patients (3/16) compared to 3.3% in renal transplant patients (1/30) [14]. Likewise, Shrader et al. found a 22.2% infection rate in HDs (2/9) compared to 10.7% (3/28) in renal transplants [15]. These studies combined SSIs and PJIs and lacked the power to determine if these rates were statistically different when stratified.

To compare organ failure patients with SOT patients for susceptibility to PJI after joint arthroplasty, infection risks of a non-functioning organ (and secondary disease) should be weighed against infection risks and disturbed wound healing caused by immunosuppressive medications. In addition to infection risks specific to each organ, the type of antibiotic prophylaxis and anesthetic could have a different influence on infection before or after SOT, which is hard to predict. Without large cohorts and prospective data, it is important to recognize the risks of infection for both groups.

To address the problem of small cohort studies, more recent studies have utilized large, publicly-available databases to adequately compare cohorts. Cavanaugh et al. used the Nationwide Inpatient Sample (NIS) database to compare 1,747 HD patients to 1,055 renal transplants [12]. They found that HD patients had higher rates of SSIs (odds ratio (OR): 2.92, 95% confidence interval (CI) 1.93 to 4.42, $p < .001$) and wound complications (OR: 2.50, 95% CI 1.41 to 4.44, $p = .002$) after TJA, when compared to renal transplant patients [12]. The authors advocated that renal transplantation be performed before TJA because this population may be associated with less postoperative complications and mortality compared to dialysis patients [12]. Similarly, Kildow et al. used 100% of the Medicare database to compare similar groups with THA [16]. They reported that patients on HD were at greater risk of PJI (OR: 6.61, 95% CI 4.25 to 10.27) at 90 days compared to patients with renal transplant [16]. This risk persisted at the two-year mark (OR: 4.47, 95% CI 3.66 to 5.47). Interestingly, patients who received a transplant had a similar PJI risk at two years compared to control patients who had only diabetes, but no organ failure. The authors concluded that diabetic patients with kidney failure should undergo renal transplant prior to THA, to optimize the surgical outcomes [16]. Similar conclusions for postoperative complications apply for patients with liver cirrhosis, and the first 90 days postoperatively appear to be critical for PJIs as early cases have been observed at a rate of 22.2% [17].

However, the risk for PJI following TKA, after SOT is 3.2 to 17.2%, and does appear higher than following THA [11,17–20]. After SOT the predominant reason for revision failure is PJI in 10% of THA, and 22.2% of TKA patients [21]. Causative microorganisms (staphylococci and streptococci) are overall similar to PJI in the general population, in which type of normal antibiotic prophylaxis should be sufficient [20]. The survivorship of revised THA after five years and ten years seem comparable with non-transplanted population regarding PJI as cause of failure (2 to 10%) [21,22]. However, there is an increased risk for aseptic loosening during the 10 to 15 years post-arthroplasty, hypothesized to be caused by decrease in graft function, and increase in organ failure, as well as the presence of higher medical comorbidities in this patient population. There is also another aspect to this question. Patients in need of organ transplant who undergo TJA and develop a subsequent PJI may lose the opportunity to undergo organ transplant because of the concern for the presence of infection in the replaced joint and the possibility of a flare-up of infection when immunosuppressive drugs are administered.

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1.7. PREVENTION: ANTIMICROBIALS (SYSTEMIC)

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QUESTION 1: Should patients with penicillin or cephalosporin allergies routinely undergo allergy testing, desensitization or a test dose before administering alternative antibiotic prophylaxis?

RECOMMENDATION: A majority of patients with a penicillin allergy can tolerate cephalosporins and do not need routine skin testing. Patients with a non-anaphylactic reaction to penicillins or cephalosporins can be given a test dose of a cephalosporin in the operating room.

STRENGTH OF RECOMMENDATION: Moderate

DELEGATE VOTE: Agree: 90%, Disagree: 8%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

A comprehensive systematic review of the literature was performed to search for all studies dealing with penicillin allergy and antibiotic prophylaxis in patients with a penicillin allergy. The search terms "penicillin allergy," "cephalosporin allergy," "antibiotic prophylaxis" and "orthopaedic" were used through February 2018 in the following search engines: Medline, Embase and Cochrane. The search terms were combined with different Boolean operators. Inclusion criteria for our systematic review were all English studies (level I to IV evidence). Exclusion criteria were non-English studies, papers more than ten years old, case reports, non-human studies, papers with less than a ten-patient sample size and papers without follow-up. The original search resulted in more than 5,000 titles. After evaluation, 27 full-text reports were read and 16 were included in this review.

According to the recommendation by the World Allergy Organization, drug hypersensitivity reactions are categorized by the timing of the onset of symptoms as immediate (i.e., develops within one hour of drug exposure) or delayed-type (i.e., onset after one hour of drug exposure) reactions. An immediate-type reaction is a true immunoglobulin E (IgE) mediated hypersensitivity, with the most common symptoms being urticaria, angioedema, rhinitis, conjunctivitis, bronchospasm or anaphylaxis and anaphylactic shock [1]. Most of the delayed-type reactions present as maculopapular exanthemas or delayed urticaria. However, severe and life-threatening reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis can also occur [2]. A penicillin allergy remains one of the most common patient-reported drug allergies, with an approximate prevalence of 8 to 12% in the general population [3–6] and is the most common patient-reported antibiotic allergy [7]. However, many studies conducted across a variety of patient populations suggest that penicillin allergy is markedly over-diagnosed [3,5,8,9]. Multiple

studies estimate that up to 90% of patients reporting an allergy are actually able to tolerate penicillin and its derivatives [3,10–15]. Reported allergies are rarely validated with proper testing, and the lack of symptom classification prevents the distinction of non-IgE-mediated reactions and true, life-threatening type I hypersensitivity reactions [8,16,17]. Furthermore, large discrepancies exist between reactions reported in patient interviews and those recorded on patient medical records [18]. Unfortunately, unconfirmed penicillin allergies remain on patients' medical records indefinitely, potentially leading to the underutilization of the entire classes of antibiotics [9,17,19]. This occurs despite recent literature showing that cross-reactivity between penicillin and cephalosporins is much lower than the alleged 10%, as administration of cephalosporin in penicillin allergic patients often only result in a reaction rate of 0.1% [20,21]. Interestingly, the IgE-mediated hypersensitivity to penicillin also decreases with time, with over half of skin test-positive patients losing sensitivity by five years and 80% by ten years [22,23]. To better establish an antibiotic regimen for patients who report an allergy to penicillin, a clear characterization of the penicillin allergy is essential. Of paramount importance is taking an appropriate clinical history for diagnosis and characterization of the patient's prior allergic reaction to penicillin [24,25].

Since history of delayed-type hypersensitivity reaction to penicillin is a contraindication to skin testing, graded dose challenge and desensitization, patients with a self-reported penicillin allergy should be questioned thoroughly about previous and current reactions to penicillin, including the route of administration, concomitant medications, the time between the dose of penicillin and the appearance of symptoms and how the reaction was managed [26].

Immediate-type hypersensitivity can only be correctly diagnosed by a skin test. It consists of a skin-prick and intradermal testing with the major determinant (penicilloyl-polylysine), the minor determinant (penicillin G), a negative control (normal saline) and a positive control (histamine). The test has a negative predictive value of 97 to 99%. Tests should be performed by a board-certified allergist [27–30]. When the skin test is negative, a confirmatory oral challenge, usually with amoxicillin, should be performed [27]. Studies by Macy et al. and Solensky et al. have shown that patients with a negative penicillin skin test are able to tolerate repeat oral doses of penicillin with low rates of resensitization [31,32]. Furthermore, the literature demonstrates that most patients (99%) with a positive penicillin skin test will still be able to tolerate a cephalosporin [33,34] Prior literature has even shown that in penicillin skin test-positive individuals who were accidently given therapeutic penicillin, only one-third to one-half have any clinically relevant reaction, meaning there are most likely high false-positive rates in skin-testing [14,35].

Since the cross-reactivity of penicillins and cephalosporins have been demonstrated to be much lower in recent literature than the purported 10%, these patients might best be tested for allergy to cephalosporin and if negative may be given a cephalosporin as prophylaxis. The optimal environment to receive an antibiotic may be the operating room under the watchful eye of an anesthesiologist, where reversal agents can be quickly administered.

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QUESTION 2: What is the alternative choice of prophylactic antibiotic when the patient has an anaphylactic allergy to penicillin/cephalosporins?

RECOMMENDATION: The choice of prophylactic antibiotic for patients with a known anaphylactic penicillin or cephalosporin allergy includes vancomycin, teicoplanin or clindamycin. Cephalosporins for patients with anaphylactic penicillin allergies may be given following skin testing.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 5%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Because gram-positive bacteria are the most common infective organisms after total joint arthroplasty, first- or second-generation cephalosporins are recommended for antibiotic prophylaxis [1]. The use of cephalosporins is usually avoided in patients with penicillin allergies because of the fear of cross-reaction between penicillin and cephalosporins, which is strongly related to the structural similarities found in their R side chains. In earlier years, the risk of cross-reaction was reported to reach 10%, but in those studies only first generation cephalosporins that may have been contaminated with penicillin were observed [2,3]. Later studies have shown that cephalosporin allergy alone is less frequent with an overall reaction rate of 2% [4]. Moreover, the cross-reaction with third- or fourth-generation cephalosporins is negligible [5]. Therefore, patients with a reported penicillin allergy should undergo skin testing, and, if the test is positive, oral challenge is recommended [6].

Patient-reported allergies have important consequences for antibiotic selection, as cephalosporin agents normally utilized for perioperative prophylaxis are avoided due to the potential for cross-reactivity, even though the associated risks are unclear [5,7,8]. Of consequence, administering suboptimal antibiotics can increase the risk for infection in these patients. Recent studies have suggested that vancomycin monotherapy is correlated with higher rates of periprosthetic joint infection (PJI) when compared to penicillin and cephalosporin regimens, presumably due to its reduced gram-negative coverage [1,9,10]. The current guidelines established by the prior International Consensus Meeting on PJI recommends that vancomycin substitution only be in cases of severe anaphylactic penicillin allergy [11,12]. However, compliance is limited by the lack of proper allergy classification [13,14].

Frequent prophylactic use of vancomycin and alternative antibiotics for penicillin-allergic patients is also associated with increased rates of infection with vancomycin-resistant *Enterococcus* (VRE), methicillin-resistant *Staphylococcus aureus* (MRSA) and *Clostridium difficile* with reduced susceptibility to vancomycin [15-18]. In a single-institution study, Lee et al. showed that patients who reported a penicillin allergy were often treated with more than one alternative broad-spectrum antimicrobial agent, including cephalosporins, fluoroquinolones, clindamycin and vancomycin [19]. Evidence suggests that over-use of broad-spectrum antibiotics leads to increased antibiotic resistance, increased clinical complications, as well as markedly longer hospital stays and costs [17,19]. In terms of public health, the presence of resistant organisms in the community further amplifies the burden of infection. Thus, it is important that vancomycin only be used for patients with true type I IgE-mediated reactions to penicillin.

If a patient presents with a true penicillin allergy, alternative antibiotics should be given (vancomycin or clindamycin are recommended in these cases) [10]. Clindamycin has an excellent oral bioavailability of 90%, though its bone penetration is not ideal, reaching 45% [20]. Moreover, clindamycin is a bacteriostatic antimicrobial agent. These characteristics make clindamycin less effective as a prophylactic antibiotic in total joint arthroplasty compared to cefazolin. Further studies are needed to gain more data. Vancomycin is a bactericidal antibiotic that penetrates well into bone, synovium, muscles and hematoma [21]. There are concerns about its use as a prophylactic antibiotic because it has a narrower spectrum of antimicrobial coverage, than that of cefazolin, and because of the potential and unnecessary risk of emerging vancomycin-resistant organisms, such as VRE or vancomycin-resistant *S. aureus*.

The data available for vancomycin used as a single prophylactic antibiotic is somewhat controversial. Tan et al. retrospectively reviewed the charts of 10,391 patients after total joint arthroplasty and found that, compared to cefazolin, vancomycin prophylaxis was associated with a decreased risk of infection with gram-positive bacteria (adjusted odds ratio (OR): 0.25, confidence interval (CI) 0.10 to 0.62, p = 0.003) and antibiotic-resistant organisms (adjusted OR: 0.10, CI 0.01 to 0.88). However, vancomycin was also associated with an increased risk of gram-negative infections (OR: 2.42, CI 1.01 to 5.82, p = 0.049) [22].

In another retrospective study, Smith et al. analyzed PJIs after switching from cefazolin to vancomycin as antibiotic prophylaxis in total knee and total hip arthroplasty. Reviewing the data of 5,036 patients, they found that PJI decreased significantly from 1% to 0.5% with vancomycin prophylaxis, and there was also a trend in the reduction of MRSA infections, but the latter change was not significant [23].

Ponce et al. reviewed the data of 18,830 elective primary arthroplasties (12,823 knee and 6,007 hip) in a retrospective study. They found, that the overall surgical site infection (SSI) rate was 2.3% with single vancomycin prophylaxis, 1.5% with the use of vancomycin and cefazolin in combination, and 1.3% with cefazolin alone. In penicillin-allergic patients, the SSI rate was 2.0% with vancomycin compared to 1% with clindamycin (p = 0.18). Non-penicillin-allergic patients had an SSI rate of 2.6% with single vancomycin prophylaxis compared to 1.6% with vancomycin plus cefazolin prophylaxis (p = 0.17), and compared to 1.3% with single cefazolin use (p < 0.01) [10].

In a prospective study, Tyllianakis et al. compared the effectiveness of vancomycin, cefuroxime and fusidic acid in total joint arthroplasty prophylaxis and found no difference in the rate of SSIs or PJIs [24].

Sewick et al. performed a retrospective study evaluating the use of a vancomycin-cefazolin combination compared to single cefazolin prophylaxis and could not demonstrate any difference in the rate of SSIs [25].

The inconsistent and controversial data about the effectiveness of vancomycin as a prophylactic agent in total joint arthroplasty may be due to its incorrect dosage. Kheir et al. demonstrated in a retrospective analysis of 1,828 patients that vancomycin was dosed correctly in only 28% of patients according to weight-based dosage recommendations [26]. Catanzano et al. showed almost the same data: evaluating 216 total joint arthroplasties 69% of the patients were underdosed, and 10% were overdosed [27].

Further studies analyzing the use of vancomycin in combination with other antibiotics and analyzing its proper dosage would be beneficial.

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QUESTION 3: What is the optimal antibiotic for perioperative prophylaxis in methicillin-resistant *Staphylococcus aureus* (MRSA) carriers who are undergoing orthopaedic procedures?

RECOMMENDATION: Vancomycin or teicoplanin is recommended as a perioperative prophylactic antibiotic agent for the current MRSA colonizer undergoing total joint arthroplasty (TJA).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

MRSA surgical site infections (SSIs) are an increasing concern after orthopaedic surgical procedures [1]. It is well-known that MRSA colonization is an independent major risk factor of MRSA SSIs [2–4]. Efforts have been made to screen for MRSA carriers and decolonize preoperatively using nasal mupirocin ointment or povidone iodine [5–7]. However, after the decolonization protocol [8,9], questions still exist as to which glycopeptide (such as vancomycin or teicoplanin) is recommended as the preferred prophylactic preoperative antibiotic for MRSA carriers [10].

Despite the vast body of literature investigating the effect of different antibiotic treatments in various kinds of surgical procedures, to the best of our knowledge, only a few studies have compared SSI rates after orthopaedic surgery among different antibiotic prophylactic regimens in MRSA carriers [11,12]. Iqbal et al. reported in a retrospective study of orthopaedic trauma patients that, among 27 MRSA carriers, none of the 5 patients who received teicoplanin developed SSIs, whereas 5 out of 22 patients who received cefuroxime developed MRSA SSI [11]. However, Gupta et al. demonstrated different results in their retrospective cohort study of veterans undergoing surgical procedures including orthopaedic surgery. They showed that vancomycin prophylaxis was not associated with a significant risk reduction of SSIs compared to other antibiotics in MRSA carriers with a relative risk (RR) of 0.61 (95% confidence interval (CI) 0.06 to 5.75) [12]. Nevertheless, both studies were retrospective observational studies with flaws that could be classify them as very low-quality.

Although little has been studied in MRSA carriers undergoing orthopaedic surgery, there are several studies that compared MRSA SSI rate between different prophylactic antibiotics in patients undergoing orthopaedic surgery regardless of preoperative MRSA colonization [13–22]. Two moderate-quality randomized controlled trials [16,17] and six low to very low-quality observational studies [14,15,18–21] compared MRSA SSI rate between glycopeptides and first or second-generation cephalosporins. Although two randomized controlled trials (RCTs) [16,17] have shown no significant difference in MRSA SSI development between glycopeptides and cephalosporins, a random effects model meta-analysis of a total of eight studies [14–21] has shown a significantly lower risk in the glycopeptide group (pooled RR: 0.29, 95% CI 0.14 to 0.62, p = 0.001, I^2 = 10%). Subgroup analysis has also revealed that, compared to cephalosporins, both vancomycin and teicoplanin demonstrate lower risks of MRSA SSI after orthopaedic surgery (RR: 0.36, 95% CI 0.15 to 0.90; RR: 0.16, 95% CI 0.04 to 0.65, respectively). Among the eight studies, three [15,18,20] compared dual prophylactic antibiotics (glycopeptide + cephalosporin) with cephalosporin alone. When a selective analysis was performed excluding these three studies, pooled RR was 0.47 with 95% CI of 0.21 to 1.05 I2 = 0%.

As a result, we recommend vancomycin or teicoplanin as a preoperative antibiotic prophylaxis for MRSA carriers, however, with a moderate level of strength due to the lack of high-quality studies performed on MRSA carriers.

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QUESTION 4: What patient factors (allergy status, weight, etc.) should be utilized to alter the choice of perioperative antibiotic prophylaxis?

RECOMMENDATION: A weight-adjusted dose of antibiotics should be administered to patients. A minimum of 2 gm cefazolin is recommended for patients with weight > 70 kg to achieve effective minimum inhibitory concentration (MIC). Vancomycin or teicoplanin should be administered in resistant-strain carriers and those with cephalosporin allergies. Patients with a penicillin allergy, irrespective of immunoglobulin E (IgE) involvement, should be given second or third-generation cephalosporins to minimize cross-reactivity.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 3%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

Perioperative antibiotic prophylaxis is one of the most effective strategies to prevent prosthetic joint infections (PJIs) following total joint arthroplasties (TJAs) [1]. Based on the profile of organisms causing early PJI, most current guidelines for perioperative antibiotic prophylaxis recommend intravenous (IV) first or second-generation cephalosporins within an hour of surgical incision, regardless of the surgery being a primary or revision TJA [2]. The recommended dose of cefazolin is 15 mg/kg which equates to 1 gm for patients who weigh less than 80 kg, whereas the standard dose for cefuroxime is 1.5 gm regardless of weight. A cefazolin dose of 2 gm and 3 gm is advised for patients over 80 kg and 120 kg, respectively [2]. However, these guidelines only provide a generalized approach to antibiotic prophylaxis [2]. In the presence of patient factors that cannot be altered, a personalized perioperative antibiotic prophylaxis with an alternative should be considered. Multiple studies provide evidence for alternative antibiotic regimens to be tailored according to carrier status, weight and allergy status.

Resistant Strain Carriers

The most common pathogens cultured in the events of surgical site infections (SSIs) and PJIs in orthopaedic surgery are gram-positive organisms, especially *Staphylococcus aureus* [1], followed by coagulase-negative *Staphylococcus epidermis* [1]. Due to the growing incidence of antibiotic resistant strains, vancomycin or teicoplanin are recommended for nasal carriers of resistant strains [2]. Although clindamycin is also an effective antibiotic against some methicillin-resistant *S. aureus* (MRSA) strains, vancomycin is a more preferred option due to its bactericidal property [1]. However, there is conflicting evidence regarding the effectiveness of vancomycin in preventing SSIs/PJIs in MRSA carriers [3–9].

No significant reduction in SSI/PJI rate was reported when cefazolin was substituted with vancomycin for MRSA carriers in two studies [3,4]. A randomized trial screened 1,028 patients undergoing TJA and identified 228 *S. aureus* carriers. There were 89 were treated with vancomycin perioperatively, whereas 139 were treated in the standard protocol group. Eight patients were MRSA carriers, but the number of MRSA carriers allocated to each group is unknown [3]. The overall PJI rate in carriers between the intervention group and non-intervention group was small (3.4 vs. 4.3%, Table 1) [3].

Five studies screened orthopaedic patients for carrier status and administered either vancomycin or teicoplanin to MRSA carriers [5–9]. The infection rate in this group of patients was compared to patients who were not screened and, therefore, did not receive vancomycin or teicoplanin. Of the five studies, four studies used vancomycin as an alternative to cefazolin [5–7,9], whereas De Lucas-Villarrubia et al. administered teicoplanin instead [8]. In contrast to the previous studies mentioned, all five studies reported a significant reduction in infection rates in patients who were given alternative antibiotics after screening compared to those who received standard protocols (Table 1) [5–9].

Weight/BMI

Patients' weight or body mass index (BMI) also dictated changes in the dosing regimen of antibiotics prophylaxis, as achieving the therapeutic dose is more difficult in obese individuals. Sharareh et al. administered 1 gm and 2 gm of cefazolin to patients weighing under and over 70 kg, respectively [10]. One-dose of preoperative vancomycin was part of the standard protocol, in which every patient was administered 15 mg/kg of vancomycin. No significant differences were observed in the number of patients achieving above cefazolin minimum inhibitory concentration (MIC) between different BMI groups. Furthermore, there was no difference in average concentration of vancomycin in bone per kilogram between the different dosage groups (Table 2) [10].

TABLE 1. Infection rates between standard antibiotics and MRSA-targeted perioperative antibiotic regimen in orthopaedic surgery

Study	Study Design	Study Number	Infection Rate	P-value
De Lucas-Villarrubia [8] (2004)	Cohort study	599 screened + teicoplanin (13 MRSA carriers) 1,228 not screened	Screened + teicoplanin = 0.03% Not screened + no teicoplanin = 0.2%	< 0.05*
Rao [7] (2011)	Cohort study	164 screened + vancomycin 345 not screened	Screened + vancomycin = 0% Not screened + no vancomycin = 3.5%	0.016*
Hadley [4] (2010)	Cohort study	1,644 screened + vancomycin (58 MRSA carriers) 414 not screened	Screened + vancomycin = 1.28% Not screened + no vancomycin = 1.45%	0.809
Kim [9] (2010)	Prospective clinical study	7,019 screened + vancomycin (309 MRSA carriers) 5293 not screened	Screened + vancomycin = 0.19% Not screened + no vancomycin = 0.45%	0.0093*
Schweizer [6] (2015)	Pragmatic study	1,122 MRSA carriers	Vancomycin intervention = 15/10000 Pre-vancomycin intervention = 32/10000	0.005*
Malcolm [5] (2016)	Cohort study	2,291 (177 MRSA carriers) screened + vancomycin 1,751 not screened	Screened + vancomycin = 0.4% Not screened + no vancomycin = 0.9%	0.04*
Sousa [3] (2016)	RCT	228 *S. aureus* carriers	Vancomycin = 3.4% Standard protocol = 4.3%	0.219

RCT, randomized control trials; methicillin-resistant *S. aureus* (MRSA)
* Denotes statistical significance at the level of $p < 0.05$.

TABLE 2. Efficacy of weight-adjusted dosing regimen in obese patients undergoing orthopaedic surgery

Study	Study Design	Study Number	First-generation Cephalosporin Concentration Administered	Outcome	P-value
Cies [11] (2012)	Retrospective case-control study	200 pediatric patients	< 70 kg = weight-based dose of cefazolin (maximum 1 gm) > 70 kg = 1 gm dose	*Rate of MSSA SSI* > 70 kg = 35.9% < 70 kg = 20.5%	0.045*
Lübbeke [12] (2016)	Prospective cohort study	9,061 patients	Cefuroxime 1.5 gm for all patients	*Rate of PJI* BMI 35–39.9 = HR=2.1, 95% CI: 1.1–4.3 Weight≥100 kg = HR=2.1, 95% CI: 1.3–3.6	 0.001* 0.003*
Sharareh [10] (2016)	Cohort study	34 patients	< 70 kg = 1 gm > 70 kg = 2 gm	*Patients above cefazolin MIC for MSSA* BMI < 24.9 = 100% BMI > 30–34.9 = 86.7% *Patients above vancomycin MIC for MRSA* < 1 gm = 86% 1.5 gm = 100%	0.19 0.80

BMI, body mass idex; CI, confidence interval; HR, hazard ratio; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; PJI, periprosthetic joint infection; SSI, surgical site infection
* Denotes statistical significance at the level of $p < 0.05$.

TABLE 3. Cross-reactivity between self-reported penicillin allergy and cefazolin in orthopaedic surgery

Study	Study Design	Study Number	Reported Allergy Rate	Number of Patients Administered Cefazolin	Adverse Reaction When Given Cefazolin
Haslam [24] (2012)	Cohort study	1,962 patients	196 patients (9.9%) IgE-mediated = 49 (25%) Non-IgE mediated = 147 (75%)	 0 54	0% in both groups
IgE, immunoglobulin E					

This was further supported by two observational studies that investigated the direct relationship between weight-adjusted cefazolin dose and the risk of SSIs/PJIs [11,12]. Cies et al. administered a standard dose of 1 gm cefazolin, irrespective of patient weight, to pediatric orthopaedic patients weighing more than 70 kg. Patients weighing less than 70 kg received weight-adjusted doses. The rate of SSI was significantly higher in the standard group (35.9 vs. 20.5%, p = 0.045, Table 2) showing efficacy of a weight-adjusted dose [11]. Lübbeke et al. reported a significant increase in the rate of PJIs in patients with BMIs greater than 35 when every patient was given 1.5 gm of cefuroxime. More specifically, there was an approximately two-fold and four-fold increase in PJI rate in patients with BMI of 35 to 39.9 and > 40, respectively, when compared to patients of normal BMI. Furthermore, patients weighing ≥ 100 kg exhibited twice the infection rate compared to patients < 100 kg (Table 2) [12]. In patients who are carriers of resistant strains or allergic to penicillin, a 15 mg/kg dose of vancomycin is recommended [13,14]. However, reaching therapeutic concentration is difficult in obese patients. Therefore, Catanzano et al. measured serum trough concentrations as a surrogate outcome of area under the curve (AUC)/MIC and reported that 60% of 216 patients were inadequately dosed [15]. Furthermore, Kheir et al. reported that only 28% of arthroplasty patients were adequately dosed with vancomycin with underdosing being more prevalent in obese patients [16].

Allergy Status

A number of studies recommend the use of second-generation cephalosporin in patients who have a penicillin allergy. This recommendation was based on a high cross-reactivity reported between first-generation cephalosporins and penicillin [2]. Studies report a cross-reactivity between penicillin allergy and cephalosporin ranging from 7.7 to 8.1% [17,18]. Saxon et al. and Kelkar et al. attributed the high rates of cross-reactivity to contamination of the drugs with penicillin during the manufacturing process [19,20]. However, other studies have shown cross-reactivity rates between 0.6 to 1% [21,22]. It is also important to note that many penicillin allergies are self-reported by patients and are often not true allergies. Hence, pre-admission skin testing for penicillin allergy may be of benefit to unmask the patients' true allergy status to administer appropriate antibiotics.

Two non-orthopaedic meta-analyses demonstrated a four-fold increase in incidence of adverse reactions when patients with penicillin allergy were given a first-generation cephalosporin instead of a second-generation cephalosporin [22,23]. Nevertheless, the absolute incidence of adverse reactions associated with first-generation cephalosporins is minimal. This was confirmed in a more recent retrospective cohort study, which found negligible adverse reactions in patients with penicillin allergy who were administered cefazolin [24]. Haslam et al. retrospectively investigated 1,962 patients, of which 196 patients self-reported as having a penicillin allergy (Table 3). There were 54 patients who were administered cefazolin and no patient reported any adverse reaction [24]. In addition, while some studies recommend clindamycin or vancomycin as an alternative to first-generation cephalosporins, superiority of clindamycin in the context of cephalosporin allergy is unclear [21,25].

Alternative Forms of Antibiotic Prophylaxis in High-Risk Patients

"Alternative" forms of prophylaxis have been suggested in patients with risk factors for PJI including intraosseous regional antibiotic administration (IORA) [26,27], dual antibiotic prophylaxis with a cephalosporin and vancomycin [28] and extended oral antibiotics [29–31]. Such regimens are postulated to provide more effective prophylaxis against PJI, but with disadvantages including increased cost, risk of side effects, concerns regarding antibiotic stewardship and promoting emergence of resistance. It has been suggested to restrict their use to patients with known risk factors for PJI, such as high BMI [32], male sex [33], diabetes mellitus [34], smoking [35], previous surgery [36] and immunosuppression [37]. Currently, there is insufficient evidence to support the use of dual or extended antibiotics in patients undergoing routine orthopaedic procedures.

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QUESTION 5: What are the indications for dual perioperative antibiotic prophylaxis in patients undergoing orthopaedic procedures? What are the optimal combinations of antibiotics?

RECOMMENDATION: In the absence of high-level data, we recommend that dual antibiotic prophylaxis should be reserved only for patients at high risk of infection, such as those undergoing revision surgery or at high risk for methicillin-resistant *S. aureus* (MRSA) infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 80%, Disagree: 15%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

A comprehensive literature review was performed to identify all studies related to the indications for dual antibiotic prophylaxis in patients undergoing orthopaedic surgery as well as the optimal combination of antibiotics. Searches for the terms "total joint arthroplasty," "orthop(a)edic," "antibiotic prophylaxis," "dual" and "combination" in various combinations and with different Boolean operators were performed through February 2018 using the search engines Medline, Embase and Cochrane. Inclusion criteria for our systematic review were all English studies (level I to IV evidence) that reported on dual perioperative antibiotics for total joint arthroplasty. Exclusion criteria were non-English language articles, studies over ten years old, non-human studies, retracted papers, case reports, review papers, studies with less than ten patients in the sample size, studies without clinical follow-up/infection rates and technique papers without patient data. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria were followed. The initial search resulted in 2,283 papers. After removal of duplicates, 201 titles were evaluated, 35

TABLE 1. Summary of studies that evaluated the efficacy of dual antibiotic prophylaxis including a beta-lactam and a glycopeptide

Author/Year	Type of Study (Period)	Type of Surgery	Antibiotic Prophylaxis (n)*	Outcome	Infection Rate (P-value)	MRSA Rate
Capdevila 2016 [22]	Retrospective cohort study (2012-2013)	Femoral neck fracture	Cefuroxime 1.5 gm induction of anaesthesia + 1.5 gm after 2h + teicoplanin 800 mg (657)	SSI according to CDC criteria	2%	0.15%
Sewick 2012 [10]	Retrospective cohort study (2008-2010)	Primary THA and TKA	Cefazolin (500) vs. cefazolin + vancomycin (1328)	SSI according to CDC criteria	1.4% vs. 1.1% (> 0.05)	0.8% vs. 0.07%
Ponce 2014 [6]	Retrospective cohort study (2005-2009)	Primary THA and TKA	Cefazolin (15422) vs. vancomycin (1500) vs. cefazolin + vancomycin (1062) vs. clindamycin (846)	SSI	1.3% vs. 2.3% vs. 1.5% vs. 1.1% (< 0.05 for cefazolin vs. vancomycin)	Information not collected
Tornero 2015 [20]	Retrospective cohort, before and after changing the prophylaxis regime (2010-2013)	Primary THA and TKA	Cefuroxime 1.5 gm induction of anaesthesia + 1.5 gm after 2h (995) vs. cefuroxime + teicoplanin 800 mg (791)	PJI according to MSIS criteria	3.5% vs. 1.3% (< 0.05)	0.5% vs. 0%
Branch-Elliman 2017 [12]	Retrospective cohort study (2008-2013)	Primary THA and TKA	Single (beta-lactam or vancomycin) vs. beta-lactam + vancomycin	SSI within 30 days	1.26% vs. 1.43% (p > 0.05)	Information not collected
Burger 2018 [18]	Retrospective cohort study (2012-2016)	Primary THA and TKA	Cefazolin (1044) vs. cefazolin + vancomycin 1 gm B45 (476) vs. cefazolin + vancomycin W45 1 gm (477)	PJI according to MSIS criteria	2.1% vs. 0.2% vs. 2.9% (p = 0.01)	0.4% vs. 0% vs. 0.3%
Liu 2014 [13]	Retrospective cohort, before and after changing the prophylaxis regime (2009-2012)	Revision TKA	Cefazolin (190) vs. cefazolin + vancomycin 1 gm (1.5 gm > 80 kg) (224)	SSI according to CDC criteria	7.89% vs. 3.13% (< 0.05)	2.63% vs. 0%

CDC, Centers for Disease Control and Prevention; MSIS; Musculoskeletal Infection Society; PJI, prosthetic joint infection; SSI, surgical site infection; THA, total hip arthroplasty; TKA, total knee arthroplasty; B45, vancomycin infusion was initiated 45 minutes before the surgical incision; W45, vancomycin infusion was initiated less than 45 minutes before the surgical incision.

* Antibiotic dose is given when the information was provided in the report.

full-text papers were read and 13 studies met the full inclusion and exclusion criteria to allow for the analysis.

While the use of first or second-generation cephalosporins is recommended as first-line perioperative antibiotics due to their broad range of pathogen coverage [1–3], patients who are proven or potential carriers of MRSA or those with a cephalosporin allergy (not penicillin allergy) may receive alternative antibiotics. For penicillin-allergic patients, the use of a third or fourth-generation cephalosporin (such as cefuroxime and ceftriaxone) with dissimilar side chains than the offending penicillin carries a negligible risk of cross-reaction [4]. The most common alternative used is vancomycin that has poor gram-negative coverage and should not be used as monoprophylaxis; and, hence its use should be combined with another antibiotic such as an aminoglycoside for gram-negative coverage. In addition, vancomycin dosing should be weight-based at 15 mg/kg [5]. Recent studies have demonstrated that vancomycin monotherapy is associated with an increased risk of infection compared with cefazolin [5,6], particularly by gram-negative organisms [7]. Furthermore, despite the reduction in the rate of MRSA infections, vancomycin should be used with caution due to the potential for the emergence of organism resistance, most notably vancomycin-resistant *enterococccus* (VRE) and vancomycin-resistant *Staphylococcus aureus* [8], and its potential for nephrotoxicity [9]. There are no randomized controlled trials, but there are several retrospective studies examining the use of dual perioperative antibiotic prophylaxis (Table 1).

Sewick et al. [10] retrospectively reviewed 1,828 primary total joint arthroplasties (TJAs) that received either a dual antibiotic regimen of cefazolin and vancomycin or received cefazolin alone in order to determine the rate of surgical site infections (SSIs) as well as the microbiology of subsequent SSIs. There were a total of 22 SSIs (1.2%) with no significant difference in the infection rate between the dual antibiotic prophylaxis group compared to the single antibiotic regimen (1.1 and 1.4% respectively, p = 0.636). However, while the addition of vancomycin to cefazolin did not decrease the rate of SSIs, it did decrease the incidence of MRSA infections (0.08 vs. 0.8% p = 0.022), but with a high number needed to treat. Ponce et al. [6], in a recent study, reported that there was no difference in SSI rate between patients receiving cefazolin monotherapy or cefazolin plus vancomycin. Elliot et al. [11] developed an economic model to explore the cost-effectiveness of vancomycin and/or cephalosporin as antibiotic prophylaxis in patients undergoing total hip arthroplasty (THA). Combination therapy (such as vancomycin plus a cephalosporin) was recommended when the rate of MRSA SSI was 0.25% or greater, and the rate of non-MRSA SSI was 0.2% or greater. Branch-Elliman et al. [12] demonstrated that dual antibiotics (beta-lactam plus vancomycin) versus single antibiotic (vancomycin or a beta-lactam) had no differences in SSI rates after total joint arthroplasty (1.43 vs. 1.26%, adjusted rate ration (RR): 1.09).

While the literature does not support the use of dual antibiotics for primary TJA, a recent study by Liu et al. [13] has demonstrated that the targeted use of vancomycin and cefazolin among patients undergoing revision total knee arthroplasty (TKA) significantly reduced the rate of overall infections (7.89 to 3.13%, p = 0.046), particularly MRSA (4.21 to 0.89%, p = 0.049). It is important to note that the author's institution had a high baseline rate of PJIs due to MRSA and methicillin-susceptible *S. epidermidis* (MRSE). Thus, there may be a potential indication to use a combination of cefazolin and vancomycin for high-risk surgical patients, including revision cases where infection risk is higher than a primary TJA or in regions or institutions with high MRSA rates.

Ahmed et al. [14] retrospectively reviewed 1,500 patients undergoing hip fracture surgery comparing the use of gentamicin plus flucloxacillin (dual antibiotics) vs. cefuroxime alone in order to evaluate the rate of deep SSIs. Paradoxically, there was an increase in deep SSIs in the dual antibiotic group compared to the cefuroxime group (2.5 vs. 1.1%), reaching statistical significance (p = 0.036).

Another precaution for using dual antibiotics is the propensity for developing acute kidney injury, which is not an infrequent situation with the use of antibiotic combinations, particularly those including gentamicin [15–17] and vancomycin [9]. It should be noted that in the study by Courtney et al. [9], dual antibiotic (vancomycin plus cefazolin) prophylaxis was found to be an independent risk factor for acute kidney injury (AKI) after primary THA/TKA (adjusted odds ratio (OR): 1.82, 95% confidence interval (CI) 1.25 to 2.64, p = 0.002). In contrast, Burger et al. [18] did not find a higher difference in renal toxicity when combination antibiotic prophylaxis was used. A potential explanation is that in the first study is that vancomycin was administered for 24 hours, while in the second study only one intraoperative dose of vancomycin was given. Since teicoplanin is less nephrotoxic than vancomycin and could be infused in < 20 minutes with a very low risk of Redman Syndrome, we consider that teicoplanin should be the glycopeptide of choice in countries that have it available. The recommended dose is 800 mg administered during the induction of anaesthesia. Since teicoplanin is not available in the USA, vancomycin would still be the first-line option. Current guidelines [2] recommend that the administration of 15 mg/kg of vancomycin (according to actual body weight) in order to obtain a serum concentration ≥ 15 mg/L until the completion of surgery. In order to avoid Redman Syndrome, it should be infused at a maximum rate of 1 gm per hour. A recent study showed that only 28% of cases received a correct dose of vancomycin [5]. The authors calculated the expected levels using pharmacokinetic equations and demonstrated that a weight-based protocol would have resulted in fewer patients having unacceptably low vancomycin levels (< 15 mg/L). Indeed, a previous study in cardiac surgery demonstrated that a dose of 20 mg/kg resulted in achieving therapeutic vancomycin levels in all patients [19]. Therefore, it is necessary to adjust the vancomycin dose based on body weight.

As mentioned above, when using dual antibiotics, teicoplanin can be used as an alternative to vancomycin. It can be infused over 20 minutes without the risk of Redman Syndrome and has a better safety profile than vancomycin. Tornero et al. [20] showed a reduction in the rate of PJIs when using teicoplanin and cefuroxime in combination was compared to cefuroxime as monotherapy (1.26 vs. 3.51%, p = 0.002). Soriano et al. [21] demonstrated similar results when evaluating antibiotic prophylaxis for patients with femoral neck fractures undergoing surgery and found that the combination of teicoplanin and cefuroxime reduced infection rates compared to cefuroxime as monotherapy (2.36% vs. 5.07%, p < 0.05). In a follow-up study from the same institution, Capdevila et al. [22] retrospectively reviewed the rate of infection in the same cohort ten years after the implementation of dual antibiotic prophylaxis in patients with femoral neck fractures and found that the rate of infection remained low at 2%.

Bosco et al. [23] demonstrated that the addition of an EGNAP (expanded gram-negative antimicrobial prophylaxis), such as gentamicin or aztreonam, to cefazolin decreased the rate of PJIs in patients undergoing primary THA but not in TKAs. This is partly because at their institution, gram-negative organisms caused 30% of the SSIs following hip procedures and only 10% of SSIs after knee procedures.

One should note the importance of timing of administration of vancomycin. Burger et al. included in their analysis the moment of starting vancomycin infusion. In one group, vancomycin administration was initiated 45 minutes before the surgical incision, and, in the other group, the infusion was initiated less than 45 minutes before the surgical incision. The infection rate was significantly

lower when the infusion of vancomycin was started earlier than the group who had the infusion closer to the start of the procedure [18].

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QUESTION 6: Should extended (beyond 24 hours) antibiotic prophylaxis be administered to patients with surgical drain(s) in place?

RECOMMENDATION: No. There is no indication for prolonged antibiotic prophylaxis regardless of the presence of surgical drains. Prolonged prophylaxis is potentially dangerous, because it increases the fraction of resistant microorganisms on the skin microbiome.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 91%, Disagree: 8%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

There is one study analyzing this question in a multicenter, double-blind randomized trial comparing a two-day-course of cefamandole-prophylaxis versus a five-day course of cephazolin-prophylaxis in 965 patients with total hip arthroplasty [1]. The rate of periprosthetic joint infections (PJIs) were similar in both groups (0.7 vs. 0.5%, not significant (NS). No significant difference was observed in the fraction of colonized drains (mean duration of drainage 3.2 ± 0.3 days). However, the number of cefamandole- and cephalozin-resistant strains was significantly higher in the long-prophylaxis group.

In two other randomized controlled trials in patients with hip and knee arthroplasty, short versus long prophylaxis was analyzed. Nelson et al. [2] reported similar infection rates, namely 3/186 (1.6%) with one-day cefazolin and 4/172 (2.3%) with a seven-day-prophylaxis in patients with hip and knee arthroplasty as well as with hip repair. Similarly, Mauerhan et al. [3] reported in a double-blind randomized trial a non-significantly lower rate with a single dose of cefuroxime 1/187 (0.5%) vs. a three-day cefazolin prophylaxis regimen 2/168 (1.2%) in patients with hip arthroplasty. In the same publication, 1/178 (0.6%) of the patients with knee arthroplasty had a surgical site infection with a single dose of cefuroxime versus 3/207 (1.4%) with a three-day course. Thus, prolonged antimicrobial prophylaxis did not prevent exogenous infections via surgical drains.

In addition, as an analogy to another field, in two trials involving patients with cardiac surgery, the effect of a prolonged postoperative antibiotic prophylaxis has been evaluated. Niederhäuser et al. [4] showed that prophylaxis until removal of the intra-aortic balloon pump did not result in a lower infection rate than regular one-day prophylaxis. Similarly, in an observational study, Harbarth et al. [5] demonstrated after adjustment for possible confounding factors, that > 48-hour prophylaxis was not associated with a decreased risk of surgical site infection as compared to ≤ 48 hours. In addition, long-term prophylaxis significantly increased the risk of acquired antibiotic resistance.

Similarly, Stefansdottir et al. [6] looked at the effect of a narrow-spectrum antibiotic prophylaxis on the skin microbiome. They showed that with three prophylactic doses of cloxacillin over a period of 12 hours, the resistance pattern of the microbiome in the groin significantly increased. The rate of methicillin-resistant coagulase negative species in the groin increased from 20% preoperatively to 50% postoperatively ($p < 0.001$).

Taken together, in several well-done studies in the field of joint arthroplasty and cardiac surgery, prolonged prophylaxis was obviously not protective and was even potentially harmful by increasing the rate of resistant strains on the skin microbiome.

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QUESTION 7: Does the presence of implants from prior surgery in the affected joint alter the perioperative antibiotic prophylaxis?

RECOMMENDATION: There is currently no evidence to suggest the use of alternate or additional perioperative antibiotics in joint surgery when prior implants exist from previous surgery. There is an increasing body of literature to suggest that conversion hip and knee arthroplasty carries a risk of surgical site infection/periprosthetic joint infection (SSI/PJI) similar to revision surgery rather than primary surgery and altering antibiotics may be one method to mitigate this risk. However, studies will need to be conducted to either confirm or refute this statement given the lack of evidence.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Hip fractures, dysplasia, femoral-acetabular impingement (FAI), slipped capital femoral epiphysis (SCFE) and Legg-Calve-Perthes disease are common reasons to undergo hip surgery with implants that eventually require conversion to total hip arthroplasty (conversion THA) [1–4]. In addition, anterior cruciate ligament reconstruction (ACLR), multi-ligamentous knee injuries, fractures and osteotomies are common reasons for prior knee surgery with implants before conversion to total knee arthroplasty (conversion TKA) [5–8]. Recent studies have demonstrated that conversion THA [3,4] and TKA [5,9] have complication rates closer to revision total joint arthroplasty (TJA) than primary TJA, including increased SSIs and PJIs. As the complications of conversion procedures become more apparent, should we change the perioperative antibiotic prophylaxis to potentially mitigate the increased risk of SSIs/PJIs?

The use of prophylactic antibiotics has been accepted as an enabling factor to successfully perform surgery in the modern era with a lower risk of surgical site infection [10]. Many prior reports, including randomized, controlled trials and a systematic review of RCTs, have reviewed the subject [11,12]. Many factors have been studied including timing, mode of delivery, dose, duration, frequency and single versus combination therapy [13]. Although we are measured as surgeons and medical centers on appropriate use of prophylactic antibiotics during routine primary arthroplasty, there remains no consensus on the presence of other implants in the affected joint and perioperative antibiotic prophylaxis in total joint surgery [11]. The recent work identifying conversion procedures at higher risk of SSIs/PJIs either used a national database [3,4] or retrospective chart review [5,9] without specification of the antibiotic prophylaxis used, assuming prophylaxis was similar to routine primary TJA.

In conclusion, it therefore seems that the standard dose/selection of perioperative antibiotic prophylaxis for primary TJA may not be adequate for conversion TJA surgery. At this time, it is unclear if the presence of prior hardware, host factors or extended operative duration required for conversion are responsible for increased complications rates, and further research will be required. Additional antibiotics [14], prolonged duration [15] or non-antibiotic adjuncts such as dilute betadine rinse [16] may be required in a similar manner to revision procedures to lower the SSI/PJI rate in conversion TJAs. In the absence of any guiding literature, we cannot recommend for or against altering perioperative antibiotics based on prior surgical

hardware before joint surgery. Further studies will be required to see what, if any, perioperative measures will help reduce SSIs/PJIs in these patients.

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QUESTION 8: Can ceftriaxone be utilized as an alternative to cefazolin in the treatment of orthopaedic infections caused by methicillin-sensitive Staphylococcus aureus (MSSA)? If so, what dosing is recommended?

RECOMMENDATION: There is minimal data in the literature evaluating the use of ceftriaxone and its appropriate dosage to treat orthopaedic infections caused by MSSA. International guidelines state that there is no consensus on the use of ceftriaxone in the treatment of prosthetic joint infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 90%, Disagree: 4%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

MSSA is a potent pathogen and a leading cause of orthopaedic infections including prosthetic joint infections (PJIs) [1]. The antibiotic standard of care therapy (SOCT) for MSSA infections includes penicillinase-resistant penicillins (nafcillin/oxacillin/flucloxacillin) with the first-generation cephalosporin, cefazolin, as an alternative [1–4]. For penicillin-allergic patients, the use of third- or fourth-generation cephalosporin or cephalosporins (such as cefuroxime and ceftriaxone) with dissimilar side chains than the offending penicillin, carries a negligible risk of cross-allergy and may be used in this specific instance for MSSA infections [5–7].

Cephalosporins are broad-spectrum antibiotics with structures based on the beta-lactam ring [8]. They are divided into generations. The first generation, which includes cefazolin (CFZ), are predominantly active against gram-positive bacteria. The third generation of cephalosporins, which includes ceftriaxone, have better activity against gram-negative organisms, but *reduced* activity against gram-positives. Ceftriaxone (CTX) is characterized by a prolonged half-life (eight hours) compared to other cephalosporins and this allows a once-daily dosing regimen [9]. This has proved convenient for certain medical indications including outpatient antibiotic therapy services [10–12]. One potential benefit of cephalosporins over penicillins is lower reported rates of adverse drug reactions for the former group of drugs in clinical studies [13,14] Weiland et al. [15] compared ceftriaxone versus oxacillin for MSSA osteoarticular infections in 124 patients and found no difference in treatment success at three to six months (83 vs. 86%, $p = 0.7$) and at > six months (77 vs. 81%, $p = 0.6$) following the completion of intravenous antibiotics. Furthermore, patients receiving oxacillin were more likely to have it discontinued due to toxicity.

The literature regarding the use of CTX as an alternative to CFZ in the treatment of MSSA infections is sparse, with only seven published studies providing direct comparison. These include five retrospective cohort descriptive studies and two prospective, double blinded, randomized controlled trials (RCTs). Of these,

three are industry-funded by the manufacturer of CTX (Roche™, Basel, Switzerland) including one of the RCTs (which will be discussed first).

Mandell et al. [16] compared the efficacy of CTX vs. CFZ against various organisms, including gram-negatives, and showed no significant difference in clinical outcomes. Gugliemo et al. [17], in a retrospective cohort study of 31 patients, compared CTX against CFZ in various dosing regimens and found no significant difference in outcomes. Tice et al. [18] reported on the outcome of treating osteomyelitis with various antibiotic regimens in another retrospective cohort study of 454 patients. Despite there being no significant differences found in any of the treatment groups (potentially due to the lack of power in the study), they concluded that the outcome supported the use of CTX.

The independent studies similarly did not show any significant difference in treatment, perhaps due to their design and lack of statistical power. Winans et al. [12], in a well-performed retrospective study comparing the efficacy of CTX against CFZ in MSSA infections, showed no differences between the groups and advised the need for a large RCT. Grayson et al. [19], in an RCT studying the outcome of treating cellulitis with either CFZ combined with probenecid to allow once daily dosing against CTX, showed no significant differences in outcome. However, this study was underpowered. Paul et al. [20] showed a higher 30-day mortality rate in patients with MSSA bacteremia treated with CTX compared to CFZ or oxacillin but again the study lacked power.

In conclusion, there are no robustly-designed or suitably-powered clinical studies to answer the null hypothesis that CTX is as effective as CFZ in treating MSSA infections.

A few experimental and animal studies, however, provide useful additional information. Cephalosporins are known to be protein bound in serum and this is thought to mediate the inoculum effect that increases their minimum inhibitory concentration (MIC). This is described by the developers of CTX based on their in vitro and in vivo data [9] and corroborated by Tawara et al. [21] in their animal study that shows that CTX has higher protein binding than CFZ and this may explain the consistently recorded MICs that CTX has over CFZ against MSSA species.

This leads onto dosing considerations. Due to the protein binding of CTX, numerous authors have suggested that higher dosing regimens are required with experimental data in support [4,21–23]. CTX is licensed at doses of 1 to 2 gm per day, but the studies above suggest that doubling this dose to 2 gm twice a day may be necessary to overcome the protein binding effect [22–24]. Nguyen et al. [25] argues that 2 gm per day is the appropriate dosing, given that the US Food and Drug Administration recommends a ceftriaxone dosage for MSSA of 2 to 4 gm per day based on pharmacodynamic analysis.

In summary, there is no robust data to support the use of ceftriaxone instead of cefazolin in the management of orthopaedic MSSA infections. Infectious diseases leaders also hold this opinion worldwide [1,25,26]. There is a need for multi-center RCTs to answer this question definitively.

Search Methodology: A comprehensive literature review was performed to identify all studies on the use of ceftriaxone in the treatment of orthopaedic infections caused by MSSA. The Medical Subject Headings (MeSH) search strategy included the following terms: ("ceftriaxone*"AND/OR "cefazolin*") AND ("MSSA*" OR "*Staphylococcus aureus*" OR "orthopaedic infections*") in various combinations and with different Boolean operators. The search engines used were: Cochrane, Embase, PubMed, Medline, Google Scholar and Web of Science. The search was conducted for studies through February 2018. Inclusion criteria for our systematic review were all English studies (level I to IV evidence) that reported on ceftriaxone use in treating orthopaedic infections caused by MSSA. Exclusion criteria were non-English language articles, studies > ten years old, nonhuman studies, retracted papers, case reports, review papers, studies with less than ten patients in the sample size, studies without clinical follow-up/infection rates and technique papers without patient data. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria were followed. The initial search results in excess of 1,000 papers. After removal of duplicates and screening of titles and abstracts, 69 full reports were assessed and reviewed.

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1.8. PREVENTION: ANTIMICROBIALS (LOCAL)

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QUESTION 1: Is there a difference in the bioavailability of vancomycin when administered through the intravenous route or intraosseous regional route in total knee arthroplasty (TKA)?

RECOMMENDATION: Yes. Tissue concentrations of vancomycin and other antibiotics are significantly higher when given via intraosseous regional administration for prophylaxis in TKA. Currently, it is unclear whether these higher concentrations will lead to a reduction in prosthetic joint infection (PJI) rates.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 91%, Disagree: 2%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Prophylaxis via intraosseous regional administration (IORA) in TKA involves injection of antibiotics into an intraosseous tibial cannula after tourniquet inflation and immediately prior to skin incision [1]. Intraosseous injection is equivalent to intravenous injection [2] but is more rapid than cannulation of a foot vein. As the tourniquet is inflated prior to injection, the antibiotic distribution is restricted "regionally" to the lower limb, similar to the manner of a "Bier's block" used in anaesthesia [3]. It allows tissue concentrations of the antibiotic to be maximized during the TKA procedure before decreasing once the tourniquet is deflated.

Earlier studies investigated the use of intravenous regional administration (IVRA) of prophylactic antibiotics via cannulation of a foot vein [4–7] and demonstrated tissue concentrations two to ten times higher than systemic administration (Table 1). The advantage of IORA is the more rapid and reliable placement of an intraosseous cannula into the proximal tibia, compared to the foot vein cannulation required for IVRA.

Vancomycin in particular may be suited for use with IORA. It covers resistant organisms commonly causing PJIs, such as coagulase-negative staphylococci and methicillin-resistant *Staphylococcus aureus* (MRSA) [8,9]. However, when given systemically it requires a prolonged infusion time [10] and can cause systemic side effects such as nephrotoxicity [10,11]. Vancomycin can be given by IORA as a bolus injection, ensuring optimal timing of prophylaxis. As distribution of the antibiotic is limited by the tourniquet, a lower vancomycin dose can be used, potentially reducing systemic side effects.

Four clinical studies have investigated the use of IORA in TKA (Table 2). One study compared 1 gm systemic cefazolin vs. 1 gm IORA cefazolin in 22 patients, reporting tissue concertation ten times higher with IORA [1]. A second study randomized 30 patients to receive either 250 mg or 500 mg of vancomycin by IORA or 1 gm of vancomycin systemically [12]. Tissue concentrations were four to ten times higher in the IORA groups. As no complications such as red man syndrome were seen on tourniquet deflation in the IORA groups, the authors recommended the use of the higher 500 mg IORA dose.

A third study randomized 22 patients undergoing revision TKA to 500 mg IORA vancomycin or 1 gm systemic prophylaxis [8]. Because revision TKA has a higher PJI rate, it was unclear if IORA prophylaxis would be effective in this setting. The presence of a tibial implant could compromise intraosseous (IO) injection, and the tourniquet is often deflated during prolonged revision procedures. The study found tissue concentrations of vancomycin 5 to 20 times higher in the IORA group and these were maintained throughout the procedure despite a period of tourniquet deflation. Concentrations from drain samples taken the next morning were similar between the groups. A fourth study randomized 22 obese patients (body mass index (BMI) > 35) undergoing TKA to 500 mg IORA vancomycin or a weight-adjusted 15 mg/kg systemic vancomycin prophylactic dose. Mean BMI was 41.1 and 40.1 (range 35 to 52) in the two groups. Tissue concentrations were five to nine times higher in the IORA versus systemic group.

It is unclear whether the higher tissue concentrations seen with IORA will reduce the incidence of PJIs. Pharmacodynamically, vancomycin's effect correlates with the area under the concentration-time curve (AUC) divided by the minimum inhibitory concentration (MIC) (AUC/MIC ratio) [9], thus greater tissue concentrations may be expected to increase efficacy. An animal study comparing six prophylaxis regimes in a murine model of TKA found IORA of both cefazolin and vancomycin to be more effective than systemic prophylaxis [13], but clinical data is lacking. As PJIs are rare, a randomized trial of IORA with PJI as the endpoint is unlikely to be feasible; larger cohort studies may offer further insights.

TABLE 1. Studies investigating the use of IVRA prophylaxis in TKA via foot vein cannulation

Study	Study Design	Patients	Findings
Hoddinott (1990) [4]	Comparative Cohort	5 patients, 1,000 mg IV cefamandole vs.750 mg IVRA cefuroxime via a foot vein in same 5 patients	Mean concentrations of cefuroxime in bone (133 mg/L) and fat (88 mg/L) were higher than those of cefamandole in bone (9 mg/L) and fat (10 mg/L); $p < 0.001$
de Lalla (1993) [5]	RCT	24 patients comparing 800 mg IV teicoplanin 2.5 hours preoperatively vs.400 mg IVRA teicoplanin via foot vein	Tissue samples (skin, subcutaneous tissue, bone, synovium) 2–10 times higher through the regional route
de Lalla (2000) [6]	Cohort	Clinical study of 160 patients (205 TKAs), 400 mg IVRA teicoplanin via foot vein	One superficial infection; no deep infections at 2-year follow-up
Lazzarini (2003) [7]	Comparative Cohort	5 patients 800 mg IV teicoplanin 2.5 hours preoperatively vs.15 patients 200 mg IVRA teicoplanin via a foot vein	Tissue samples (skin, subcutaneous tissue, bone, synovium) 2 times higher through the regional route

IV, intravenous; IVRA, intravenous regional administration; RCT, randomized control trial; TKA, total knee arthroplasty

TABLE 2. Studies investigating the use of IORA prophylaxis in TKA

Study	Study Design	Patients	Findings
Young (2013) [1]	RCT	22 Primary TKA patients, 1 g systemic cefazolin vs. 1 gm IORA	Mean cefazolin subcutaneous fat concentrations: 11 ug/gm systemic vs.186 ug/gm IORA, mean bone concentrations: 11 ug/gm vs.130 ug/g IORA
Young (2014) [12]	RCT	30 Primary TKA patients, 1 gm Systemic vancomycin vs.250 mg and 500 mg IORA	Mean vancomycin fat concentrations: 3.2 ug/g systemic group, 14 ug/gm 250 mg IORA group, 44 ug/gm 500 mg IORA group. Mean bone concentrations: 4.0 ug/g systemic, 16 ug/gm 250 mg IORA, 38 ug/gm 500 mg IORA
Young (2017) [8]	RCT	20 Revision TKA patients, 1 gm systemic vancomycin vs. 500 mg IORA	Mean vancomycin concentrations fat: 3.7 ug/gm systemic vs.49.3 ug/gm IORA, mean bone concentrations: 6.4 ug/gm vs.77 ug/gm IORA
Chin (2018) [14]	RCT	22 Primary TKA patients with BMI > 35, 15 mg/kg systemic vancomycin vs.500 mg IORA	Mean vancomycin concentrations fat: 4.4 ug/gm systemic vs. 39.3 ug/gm IORA, mean bone concentrations: 6.1 ug/gm vs. 34.4 ug/gm IORA
Young (2015) [13]	Animal Model	42 mice, 6 prophylaxis regimes compared	IORA of vancomycin and cefazolin more effective than systemic in preventing PJI in murine model of TKA infection

BMI, body mass index; IORA, intraosseous regional administration; TKA, total knee arthroplasty; RCT, randomized controlled trial

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QUESTION 2: Can local antibiotic delivery alone be effective in the treatment of musculoskeletal infections?

RECOMMENDATION: At the present time and without further refinement of delivery mechanisms and improved pharmacokinetics, local antibiotic alone is not believed to be sufficient for the management of patients with orthopaedic infections. Other adjunctive treatment modalities need to be combined with local delivery of antibiotics.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 91%, Disagree: 6%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Musculoskeletal infections comprise a broad range of conditions with varying presentations and conditions, including the presence of implants. Disregarding necrotizing infections of muscles, which are a specific disease, bone and joint infections have in common a well-known difficulty in obtaining eradication, particularly when associated with an implant. Biofilm formation [1–7], the development of certain phenotypical variants, such as small colony variants and intracellular persisters [7–16], and leucocyte dysfunction in the close vicinity of the surface of implants [17], are among the most important causes of identified microbial resistance.

Systemic antibiotic treatment with duration of 6 to 12 weeks is usually recommended for non-tuberculous bone and implant-related infections [18–20], along with surgical debridement, to overcome persistence and potential relapse. There are, however, issues regarding the complexity of pharmacokinetics of antibiotics in bone, with consequences not fully understood yet [21,22]. However, local delivery could provide continuous release in all affected compartments, optimizing the effect of most antibiotics, as time of exposure at adequate concentrations is the most important pharmacodynamic parameter for all antibiotic classes, except aminoglycosides, quinolones and some newer agents [23,24].

In vitro experiments are ideal to study the effect of a single parameter, such as the effect of antibiotics in isolation. The main difficulty resides in creating realistic conditions that allow transposing the observations in vivo [6]. It is known that biofilm is a complex structure that matures over time [1,6]. It is also known that mature biofilm is much more difficult to eradicate than biofilm of 24 hours age or less [25–28]. Considering the time course of musculoskeletal infections, only experiments studying biofilm matured over more than 48 hours would be of interest. The structure of biofilm also is influenced by the surrounding physicochemical conditions, and its density increases with external stress [6,29–32]. The exact conditions in vivo are, however, not fully measurable nor understood and probably have important variability [6], but there are nonetheless physicochemical stresses acting on biofilm formation such as the host immune system. Thus, publications describing dynamic conditions are probably more valuable than those describing static conditions only. Prolonged exposure to antibiotics increases susceptibility of biofilm bacteria to antibiotics [33]. Studies examining short exposure to antibiotics with time-dependent killing effect overestimate resistance of biofilm.

A thorough search of the literature using both PubMed and Google Scholar for prolonged exposure to antibiotics (> 72 hours) of matured biofilm (> 48 hours), complemented by cross-referencing, identified the studies listed in Table 1 [34–38]. While thousands of biofilm eradication have been published, only a very small number tested matured biofilm or antibiotic exposure long enough to obtain not only a reduction of bacterial counts but complete eradica-

tion. Only a limited number of combinations of bacterial strains and antibiotics have been investigated in these studies, but it has been proven that matured biofilm can be potentially eradicated solely by prolonged exposure to antibiotics.

Required concentrations, however, are higher and exposure times longer than those obtained from carrier materials currently available [39–41]. For many antibiotics, stability in aqueous solution and at body temperature also is limiting for local application [42]. Continuous or repeated exogenous administration of antibiotics would be necessary to reach the required time and concentration profiles. Further studies indicate that the effect of antimicrobial drugs can be enhanced by the use of synergistic combinations of antibiotics [43–45] or by the addition of antibacterial peptides [46–48], quorum-sensing inhibitors [49], biofilm-dispersing drugs [50–52] or nitric oxide [46]. Of note, the addition of ethylenediaminetetraacetic acid (EDTA) already is applied in antibiotic lock solutions for treatment of catheter-associated infection [53]. Also, n-acetylcysteine is utilized in the treatment of pulmonary infection in cystic fibrosis, a biofilm-associated disease without implant, to disperse biofilm and enhance the effect of co-administered antibiotics [52,54]. But clinical application of these chemicals for treatment of musculoskeletal or implant-associated infections has not been described.

Some studies of catheter-related infections in animal models confirm the in vitro observations, as biofilm within the catheter could be eradicated by antibiotics in combination with biofilm dispersing drugs. The main issue, however, is that in some of these studies systemic antibiotics also had to be administered to prevent sepsis associated with the infected catheter system. In a mouse model, 48 to 72 hour-old *S. aureus, E. coli* and *P. aeruginosa* biofilm could be eradicated within a port system by the sole action of local antibiotics combined with additives such as EDTA or L-arginine [50,55]. These observations could be confirmed even in immunosuppressed animals, but microbiological workup was limited to biofluorescence. Eradication could also be obtained with daptomycin in an infected rat model using five-day-old staphylococcal biofilm, with a potential regrowth phase of up to seven days followed by sonication [56].

The focus of orthopaedic research has been mainly related to development and application of carrier materials that resorb in situ, in order to circumvent the known insufficiencies and disadvantages of bone cement that is currently the most preferred method of delivery of local antibiotics. Particularly, bone cement can act as a foreign body recolonized by biofilm after the initial peak release of added antibiotics [57,58]. Antibiotics have been applied locally without any carrier material or with collagen, calcium sulphate based materials in combination with calcium phosphate/calcium carbonate/hydroxyapatite, hyaluronic hydrogels, or with polymers as carrier. Bone allograft can also be used successfully as carrier for antibiotics.

Local administration of powdered antibiotics on a large scale was explored during World War II, in the very beginning of the era of antibiotics [59,60]. There is only one randomized clinical trial, which included 907 patients who underwent both instrumented and non-instrumented spinal surgery in India [61]. All patients received systemic prophylaxis with intravenous cefuroxime, the intervention group also receiving 1 gm of topical vancomycin. No significant difference in the rate of surgical site infection (SSI) between the control (1.68%) and treatment (1.61%) groups could be identified. But in the absence of a carrier material delaying absorption, the antibiotics can be expected to be eliminated rather rapidly from the surgical site to be effective.

A different strategy for local antibiotic delivery is continuous irrigation with a catheter, although it has also been reported in conjunction with surgical debridement. Its main advantage is that the agent can be switched and constant concentrations can be maintained. Only degradation of the drug in the solution to be infused has to be considered [42]. Reported success rates vary from 18 to 85% [62–65]. Only one study examined isolated local antibiotic administration without debridement [62]. In the only modern study, primary implants thus treated did not experience relapse and recurrence of infection was seen in all but one megaprosthesis patients [65]. This study, however, included only 12 subjects [65]. Successful eradication was observed in patients with a short duration of symptoms, susceptible gram-positive organisms, absence of a sinus tract and no prosthetic loosening [63].

In prophylaxis, there is good evidence supporting local antibiotic administration. A systematic review demonstrated that the local application of antibiotics significantly reduced the infection rates in case of open long bone fractures, regardless of what carrier material was used or after sternotomy [66], when applying collagen fleece with gentamicin [67]. The benefit of the addition of antibiotics to bone cement in primary total knee arthroplasty to prevent postoperative infection has also been shown in a randomized trial, including 340 patients ($p = 0.024$) [68]. In two very recent randomized trials, antibiotic-loaded hydrogel showed a significant reduction of SSI in 380 cases of primary or aseptic revision arthroplasty ($p = 0.003$) [69], as well as in 253 cases of internal fixation of closed fractures ($p < 0.03$) [70]. Also, calcium sulphate/calcium carbonate loaded with gentamicin, implanted at the second stage of septic revision total knee arthroplasty, showed a reduction in reinfection rate, comparing two groups of 28 patients in a retrospective study [71]. But, as discussed above, this favorable effect might be lost in treatment of established biofilm.

There is a paucity of data providing comparative evidence regarding the use of local antibiotics in treatment of biofilm-associated musculoskeletal infections. In a randomized trial on 30 patients, comparing calcium sulphate with bone cement as antibiotic carrier and filler material, cure rates for chronic osteomyelitis were similar, but the resorbable material did not require a second operation for removal [72]. A retrospective study of 65 cases of chronic osteomyelitis, comparing calcium sulphate loaded with tobramycin to debridement without filler material, identified a significantly better healing rate in the local antibiotic treatment group [73]. Interestingly, management of dead space around the bone in chronic osteomyelitis with S53P4 bioglass that has mild intrinsic antimicrobial activity even without antibiotics showed comparable results to calcium-based antibiotic-loaded carriers in 2 retrospective studies with a total of 101 patients [74,75]. In a large study investigating an absorbable, gentamicin-loaded, calcium sulphate/hydroxyapatite biocomposite in chronic osteomyelitis in 100 patients with poor Cierny & Mader hosts and Type III and IV chronic osteomyelitis, infected non-union and concomitant septic arthritis, showed a low infection recurrence rate of 4%, which is much lower than the expected recurrence rate in this group of patients [76].

Local application of antibiotics carries some adverse effects. Calcium-containing carrier materials can induce life-threatening hypercalcaemia [76–78]. The exact incidence of this complication is unknown. Despite the frequent use of calcium-based antibiotic carriers, with case series reporting hundreds of patients in total [39,79-81], hypercalcaemia is reported only in isolated cases. Antibiotic release can also be rapid and reaching toxic serums levels [82]. This can also be the case with calcium sulphate, depending on the quantity used, the total dose of antibiotics and the renal function of the patient [83].

In summary, there are no randomized clinical trials or other high-quality studies demonstrating that the use of local antibiotics alone has a role in the management of musculoskeletal infections.

TABLE 1. List of publications identified studying the effect of prolonged exposure (> 72 hours) to antibiotics on matured biofilm (> 48 hours old)

Microorganism	Biofilm Age and Substrate	Antibiotics	Test Conditions	Conclusions	Reference
Staphylococcus aureus UAMS-1	7 days old Titanium-aluminium-niobium discs	Vancomycin up to 2,000 mg/l	Static and shaking Sonication	Vancomycin ≥ 200 mg/l eradicated biofilm within 28 days under static conditions. No eradication could be obtained within 28 days under shaking conditions.	Post et al. *J Orthop Res* 2017[34]
Staphylococcus aureus ATCC 6538 and ATCC 43300 *Staphylococcus epidermidis* ATCC 35983 and ATCC 12228	4 days old Polycarbonate discs	Ceftobiprole, vancomycin, daptomycin, rifampin, and combinations of ceftobiprole + rifampin and vancomycin + rifampin, at various clinical concentrations	Static Vortexing	No more biofilm could be detected after 7 days exposure in certain combinations of strains and antibiotics. As only vortexing was performed for recovery cultures, sensitivity of the study is suboptimal and this limits interpretation of results.	Abbanat et al. *Int J Antimicrob Agents* 2014[38]
Staphylococcus aureus methicillin-resistant, clinical strain *Staphylococcus epidermidis*, methicillin-resistant, clinical strain *Enterococcus faecalis* clinical strain *Enterococcus faecium* clinical strain	7 days old Silicon tube	Vancomycin 50 mg/l or linezolid 5 mg/l 14 days exposure	Continuous flow Regrowth phase of 7 days	Both MRSA and MRSE biofilms could be eradicated by both antibiotics within < 5 days treatment. Enterococcal biofilm could not be eradicated under the conditions of the experiment.	Bayston et al. *Antimicrob Agents Chemother* 2012[37]
Cutibacterium. acnes clinical strain	6 days Titanium discs	Penicillin G 12 mg/l, linezolid 20 mg/l with or without rifampin 8 mg/l	Rolling Regrowth phase of 9 days	After 14 days treatment with penicillin G or with a combination of linezolid with rifampin, biofilm was eradicated, without late relapse.	Bayston et al. *J Antimicrob Chemother* 2007[36]
Pseudomonas aeruginosa, 23 clinical strains	12 days old Polystyrene pegs	Tobramycin 4 mg/l and/or clarithromycin 200 mg/l 28 days exposure	Static Sonication	6/23 *P. aeruginosa* biofilm eradicated after 28 days treatment by tobramycin with or without addition of clarithromycin. Synergistic effect of tobramycin with clarithromycin in 9/23 strains. No eradication by clarithromycin alone.	Tré-Hardy et al. *Int J Antimicrob Agents* 2009[35]

MRSA, methicillin-resistant *S. aureus*; MRSE, methicillin-resistant *S. aureus*

Local antibiotics, regardless of the carrier, may have a role in the management of some musculoskeletal infections when combined with surgical intervention and administration of systemic antibiotics. The available local delivery systems in clinical practice are inadequate to allow reaching high enough local concentrations of antibiotics that can eliminate mature biofilms. Further developments are necessary to obtain delivery vehicles that can reach very high local concentrations of antibiotics for a duration long enough to be effective. Considering the heterogeneity of musculoskeletal infections and the variability of treatment protocols [18–20] with adverse effects associated with administration of antibiotics [84], large-scale studies are needed to examine the role of local antibiotics as sole treatment modality in biofilm-associated musculoskeletal infections.

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QUESTION 3: Does the local administration of vancomycin powder to a wound during surgery reduce the risk of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)? If so, what are the risk factors associated with its use?

RECOMMENDATION: No. There are no high-quality studies on vancomycin powder for the prevention of PJIs. The abundance of retrospective spine literature suggests that vancomycin powder reduces the incidence of surgical site infections. However, the only published randomized control trial (RCT) suggests that is has no impact.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 6%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Local delivery of antibiotic powder has been used with the goal of delivering a high concentration of antibiosis to the wound site without risk for systemic effects. This method has been used with some success in other surgical fields, in particular abdominal surgery prior to the existence of safe and effective systemic antibiotics for prophylaxis [1]. However, vancomycin powder has gained widespread acceptance for prevention of SSIs in spinal surgery.

TABLE 1. Spine literature on vancomycin powder

Author	Year	Category	Procedure	Study Design	Sample size	Infection Outcome	Infection Rate*	OR
Tubaki	2013	Spinal Surgery	Spinal fusion, all levels	Prospective; RCT	907	Superficial and deep	1.6% vs. 1.7%	0.96
Dennis	2016	Spinal Surgery	Instrumented spinal fusion	Retrospective; Consecutive	389	Superficial and deep	0.8% vs. 6.3%	0.13
Gaviola	2016	Spinal Surgery	Multilevel spinal fusion	Retrospective; Consecutive	326	Superficial and deep	5.2% vs. 11%	0.26
Ross	2016	Spinal Surgery	Lumbar fusion	Retrospective; Consecutive	210	Deep	0% vs. 5%	0.13
Martin	2015	Spinal Surgery	Posterior cervical fusion	Retrospective; Consecutive	289	Deep	5.2% vs. 6.9%	0.74
Theologis	2014	Spinal Surgery	Multilevel spinal fusion for deformity	Retrospective; Consecutive	215	Superficial and deep	2.6% vs. 10.9%	0.22
Hill	2014	Spinal Surgery	Posterior spinal fusion, all levels	Retrospective; Consecutive	300	Superficial and deep	1.5% vs.5.5%	0.44
Emohare	2014	Spinal Surgery	Posterior thoracolumbar fusion	Retrospective; Consecutive	303	Superficial and deep	5.2% vs. 5.8%	0.89
Godil	2013	Spinal Surgery	Posterior spinal fusion for trauma	Retrospective; Consecutive	110	Superficial and deep	0% vs. 13%	0.06
Schroeder	2016	Spinal Surgery	Spinal fusion, all levels	Retrospective; Pre-post	3477	Deep	0.4% vs. 1.3%	0.30
Heller	2015	Spinal Surgery	Posterior instrumented fusion	Retrospective; Pre-post	683	Superficial and deep	2.6% vs. 5.3%	0.48
Tomov	2015	Spinal Surgery	Spinal fusion, all levels	Retrospective; Pre-post	3598	Superficial and deep	1.3% vs. 2.4	0.53
Martin	2014	Spinal Surgery	Thoracolumbar fusion for deformity	Retrospective; Pre-post	306	Deep	5.1% vs. 5.2%	0.96
Strom	2013	Spinal Surgery	Posterior cervical fusion	Retrospective; Pre-post	171	Superficial and deep	2.5% vs 10.9%	0.21
Kim	2013	Spinal Surgery	Spinal fusion, all levels	Retrospective; Pre-post	74	Superficial and deep	0% vs. 12.5%	0.09
Strom	2013	Spinal Surgery	Lumbar fusion	Retrospective; Pre-post	253	Superficial and deep	0% vs. 11%	0.02
Caroom	2013	Spinal Surgery	Posterior cervical instrumented fusion	Retrospective; Pre-post	112	Superficial and deep	0% vs. 15%	0.07
Pahys	2013	Spinal Surgery	Posterior cervical procedures	Retrospective; Pre-post	2001	Deep	0% vs. 1.9%	0.13
Rahman	2011	Spinal Surgery	Multilevel spinal fusion for deformity	Retrospective; Pre-post	920	Deep	0.7% vs. 5%	0.14
Sweet	2011	Spinal Surgery	Posterior thoracolumbar instrumented fusion	Retrospective; Pre-post	1732	Deep	0.2% vs. 2.6%	0.08
Singh	2015	Trauma	Tibial plateau and pilon fracture ORIF	Retrospective; Consecutive	93	Deep	10% vs. 16.7%	0.55
Yan	2014	Shoulder and elbow	Open release of traumatic stiff elbow	Retrospective; Consecutive	272	Superficial and deep	0% vs. 6.5%	0.04
Wukich	2015	Foot and ankle	Foot and ankle surgery in diabetics	Retrospective; Pre-post	162	Superficial and deep	4.9% vs. 18.5%	0.27
Omrani	2015	Adult reconstruction	Total hip arthroplasty	Retrospective; Consecutive	125	Superficial and deep	NA	NA

OR, odds ratio; ORIF, open reduction and internal fixation
*Intervention vs. control infection rate

The use of powdered intra-wound vancomycin became routine practice in spinal surgery based on evidence from more than 20 retrospective studies, which demonstrated its efficacy (Table 1) [2–3]. However, many of these retrospective studies were performed with a pre- and post-intervention study design, in which the current practice of administering topical vancomycin powder was compared to an historical control [4–5]. Furthermore, 8 retrospective studies reported SSI rates above 11% for the control group [4,8–10,17,19–21]. It is likely that a publication bias contributed to the consistency of the positive signal of efficacy in retrospective studies. However, the only randomized trial did not demonstrate a reduction in risk for surgical site infection with vancomycin powder [6].

There is not enough evidence to support the use of topical vancomycin powder outside of spine surgery. A single retrospective study on 125 patients undergoing primary total hip arthroplasty demonstrated fewer infections for patients receiving both intra-wound and intravenous vancomycin compared to patients receiving only systemic prophylaxis [7]. Small studies on tibial plateau or pilon fractures and reconstructive foot and ankle surgery have demonstrated a modest improvement with topical antibiotics [8].

While the efficacy of topical vancomycin remains in question, it appears that there have been few adverse effects from its use in spinal surgery. A systematic review reported only 23 complications in 6,700 patients, most commonly seromas [9]. However, there have been case reports of renal insufficiency, circulatory collapse and hearing loss that were attributed to topical vancomycin [10–11]. It is difficult to assess the contribution of topical vancomycin to bacterial resistance. The short-term exposures from topical vancomycin may be insufficient for the emergence of resistant bacteria and no cases have yet been reported in the spine literature. However, surgeons must weigh the potential benefits of topical vancomycin against the theoretic risks of overexposure that could increase the prevalence of resistant bacterial strains.

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QUESTION 4: Is there a role for the use of antibiotic-loaded carriers (calcium sulfate/calcium phosphate (CaS/CaP) in the treatment of surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: The use of antibiotic-loaded carriers, specifically CaS and CaP based materials, to locally deliver antimicrobials at sites of musculoskeletal infection, specifically SSI and PJI, have not been shown to have any beneficial effect in the management of SSI/PJI.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 80%, Disagree: 13%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Patient care for biofilm-based and/or implant-associated infections typical of SSIs and PJIs presents the need for antimicrobial therapy, dead space management, and bone defect reconstruction. Besides the radical surgical debridement, administration of local and systemic antibiotics is an important part of management of PJIs [1].

The application of the local antibiotic therapy was championed by Buchholz et al. at the Endo Klinik in 1984 with the development of antibiotic-loaded acrylic cement (ALAC) [2]. Numerous other antibiotics carriers have been developed. A potentially useful group are the synthetic resorbable CaS and CaP compounds. There are currently four commercial ceramic bone substitutes with approved (CE-marked) use as carriers of antibiotics. These carriers have different material formulations, degradation profiles and are loaded with different antibiotics with different dosage. Two of the products are pre-set beads and two carriers are injectable. The injectable carriers are biphasic composites where hydroxyapatite particles are surrounded by an in situ setting calcium sulfate.

In vitro studies have shown that the very high local concentrations achieved with local antibiotic carriers can have an effect on biofilm, which is a major issue in PJIs [3,4]. A single recommended daily antibiotic dose incorporated into a biphasic resorbable carrier has been reported to result in local antibiotic levels

of 100 to 1,000 times of the minimum inhibitory concentration (MIC) for the first few days and is sustained above the MIC for up to four weeks [5]. The elution occurs from the resorbing calcium sulphate material, from both bulk and surface which makes the elution complete and no antibiotics are trapped, nor is the release maintained over time at sub-inhibitory levels as with polymethyl methacrylate (PMMA), which may induce antibiotic resistance [6], ototoxicity and nephrotoxicity [7], if patients already are suffering from renal insufficiency.

Surgical Site Infection

In regard to SSI, this systematic review resulted in nine studies (Table 1). Most of these were retrospective studies with low levels of evidence. McNally et al. [8] reported a consecutive prospective series of 100 patients using a biphasic CaS/apatite carrier with gentamicin in a one-stage procedure in the treatment of longstanding chronic osteomyelitis with an infection eradication in 96% of the patients at a mean follow-up of 19.5 months.

In a long-term retrospective study of 65 patients using plain preset calcium sulphate beads (OsteoSet-T, Wright Medical (now Microport), Memphis, Tennessee) in the treatment of adult chronic osteomyelitis, no significant differences were observed in the healing rates between debridement with calcium sulphate beads (80% healing) and debridement alone (60% healing), at a mean follow-up time of 75 months [9]. However, in a subgroup of 39 patients with medullary osteomyelitis and a normal immune system (Cierny-Mader classification IA), 17 patients with debridement and calcium sulphate beads and 22 patients with debridement alone, the difference in healing rates was statistically significant in favor of using calcium sulphate beads and debridement ($p < 0.05$) [9]. In a larger retrospective series of 193 patients using calcium sulphate beads in chronic osteomyelitis the eradication rate was 90.8% at a mean follow-up of 44 months [10].

In a retrospective study of 27 patients, the use of bioactive glass S53P4, PerOssal (BonAlive Biomaterials, Turku, Finland) or a mixture of tricalcium phosphate and an antibiotic-loaded demineralized bone matrix in chronic osteomyelitis of the long bones showed no differences between the groups and healing rates surpassing 80% at a mean follow-up time of 21 months [11].

In a prospective study using Herafill (Heraeus Medical, Hanau, Germany), a preset carbonate sulphate composite in the treatment of osteomyelitis reported on infection eradication in 16 out of 20 patients at a mean follow-up of six months [12]. Smaller series of patients show consistently higher success rates [13–15].

TABLE 1. Included studies for SSI

Author	Year	Study Design	Number of Patients	Mean Follow-Up (Months)
McNally [8]	2016	Prospective case series	100	19
Fleiter [21]	2014	Prospective open label phase 2	20	6
Von Stechow [22]	2009	Prospective case series	20	12
Drampalos [23]	2017	Retrospective	12	4
Ferguson [10]	2014	Retrospective	195	42
Humm [15]	2014	Retrospective	21	15
Romano [11]	2014	Retrospective	27	22
Chang [9]	2007	Retrospective	65	75
McKee [16]	2010	Prospective RCT	30	38

RCT, randomized clinical trial; SSI, surgical site infection

TABLE 2. Included studies for PJI

Author	Year	Study Design	Number of Patients	Mean Follow-Up (Months)
Logoluso [18]	2016	Prospective case series	20	12
McPherson 19]	2013	Prospective trial	250	12
Flierl [21]	2017	Retrospective	32	12.7
Kallala [20]	2015	Retrospective	15	16
Sakellariou [17]	2015	Prospective trial	46	36

PJI, periprosthetic joint infection

Clinical studies consistently reported that approximately 5 to 15% of the patients treated with calcium sulfate carriers developed a seroma and fluid drainage, but as much as 32% was reported by McKee et al. [16]. A composite carrier consisting of calcium sulfate/hydroxyapatite has reduced the occurrence of sterile drainage to 6% [8].

There is one randomized controlled trial on the use of antibiotic-loaded ceramic carrier, where calcium sulfate (CS) beads were used in the treatment of chronic osteomyelitis and infected nonunion with standard antibiotic-impregnated PMMA beads as control [16]. In addition to demonstrating an equivalent rate of infection eradication (86% at 24 months mean follow-up), the ceramic beads decreased the rate of secondary surgical procedures significantly (7 CS vs. 15 PMMA, $p = 0.04$) required for PMMA bead removal and bone grafting.

Ferguson et al. [10] described tobramycin-loaded calcium sulfate in the treatment of 195 cases of chronic osteomyelitis. They demonstrated clinical efficacy but had a clinically relevant wound discharge problem in over 15% of cases. The rapid dissolution of the plain calcium sulphate beads does produce a seromatous reaction.

Perirprosthetic Joint Infection

Focussing on PJIs, there is a paucity of robust data in the literature (Table 2). Combinations of cement spacer and calcium sulfate/phosphate carrier of antibiotics showed significantly lower recurrence rate ($p < 0.05$) in the group receiving the carrier (6.6%) compared to the group with cement spacer alone (16.1%) [17].

The use of CERAMENT G or CERAMENT V (Bonesupport, Lund, Sweden) as a coating on implants in infected revisions has shown initial implant stability in a limited 20 patient study with no signs of radiographic loosening at a mean follow-up of 12 months [18].

The largest retrospective cohort study was performed by McPherson et al. This described the use of calcium sulfate beads loaded with antibiotics in 250 cases after two-stage prosthetic revision with the use of PMMA. The rate of wound drainage in this series was 3.2% [19].

Flierl et al. described the use of plain calcium sulfate beads in 33 patients undergoing debridement and implant retention of infected total knee and hip arthroplasties. The success rates were not better than the established success rates for this procedure in the literature. The authors concluded that there is currently no indication for their use based on a lack of evidence of their efficacy in the literature and their significant cost [12].

Kallala et al. reported on 15 patients who had undergone revision procedures for PJIs incorporating antibiotic-loaded calcium sulfate beads. They noted postoperative hypercalcemia in three patients (18%) and in one case this required treatment. This metabolic disorder was attributed to the rapid dissolution and absorption of the plain calcium sulfate beads typically seen with this product. They alerted surgeons to this potentially dangerous side effect [20].

There is currently no high level of evidence study that proves that the use of absorbable material containing antibiotics influences the outcome of surgical management of patients with PJIs. The low number of studies and low levels of evidence of the included studies are the major limitations. Due to heterogeneous cohorts, large differences in the patients' conditions, variations in material composition, the form and administration of the materials (pre-set or injectable), the variation in antibiotics used as well as the dosage, makes comparison between the materials difficult and not possible to draw conclusions.

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QUESTION 5: Can fresh-frozen allograft (FFA) be used as a carrier to deliver local antibiotics during revision arthroplasty?

RECOMMENDATION: Emerging evidence suggests that specialized preparations of antibiotic-impregnated allograft are more effective than FFA mixed with antibiotics.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 63%, Disagree: 14%, Abstain: 23% (Super Majority, Weak Consensus)

RATIONALE

Bone allograft is one of the reconstructive options that can be used during revision arthroplasty. However, there are risks of bacterial colonization due to the fact that allografts are non-vascularized, and so they are not suitable for use alone during the management of periprosthetic joint infections (PJIs). The addition of antibiotics to bone cement is one method to potentially reduce the risk of PJIs and surgical site infections (SSIs). However, another factor that must be taken into account in such situations is the role of the biofilms. Formation of biofilms on implant surfaces enables bacteriae to evade the host immune system, as well as to attenuate the effectiveness of antibodies. Biofilm-embedded bacteria, therefore, require higher concentrations of antibiotics for elimination, in comparison to their planktonic counterparts [1,2].

The antibiotic-carrying capability of allograft far exceeds that of bone cement [3–5]. A number of studies have reported on the use of FFAs mixed with antibiotics during revision surgery for PJIs [5–7]. These studies support the use of FFAs as an antibiotic carrier in aseptic revision arthroplasty and in the second stage of two-stage revisions. However, in such situations, only antibiotics in powder form can be added to FFAs which limits the choice of antibiotics. Another drawback of FFAs applies to the local tissue effect of the high local antibiotic concentrations. While some antibiotics (e.g., vancomycin or tobramycin) are tolerated very well, others show a deleterious effects on osteoblasts (e.g., ciprofloxacin) [8–10]. Nevertheless, FFAs with antibiotic powder mixed have been used clinically in sites without evident florid infection as a more prophylactic tool [5]. The generated concentrations show a burst release for some days that appear sufficient for avoiding bacterial colonizations. However, the concentrations are not maintained for a prolonged period of time, which is necessary for eliminating chronic infections mediated by biofilms [11,12].

This has led to the development of specially-prepared allografts that are more suitable for one-stage revisions, due to their ability to provide the necessary high antibiotic concentrations for prolonged durations [13,14]. The use of these antibiotic-loaded allografts may be considered safe and incorporation of allografts into the host bone seems to not be impaired [5,7,15]. The removal of bone marrow (i.e., fat and cellular components) in such allograft preparations improves the safety of allograft due to immunological reactions, increases the antibiotic storage capacity of the graft and aids better incorporation of allograft into the host bone. Other investigators have demonstrated that antibiotics bonded to bone grafts avoid bacterial colonization and biofilm formation, thereby enhancing osteogenesis and integration of the graft and implant [16,17]. However, published literature on the clinical use of such allograft preparations is limited and further studies are necessary to determine their long-term effectiveness [18].

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1.9. PREVENTION: SURGICAL SITE PREPARATION

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QUESTION 1: Does preoperative skin cleansing at home prior to orthopaedic surgery have a role in the reduction of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Yes. Preoperative skin cleansing at home prior to orthopaedic surgery does have a role in the reduction of subsequent SSIs/PJIs. Specifically, chlorhexidine gluconate (CHG) has been shown to have excellent results in preventing PJIs/SSIs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 5%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

As noted by the Centers for Disease Control and Prevention, preoperative skin cleansing with an antiseptic agent can substantially decrease skin microbial counts [1,2]. Studies examining this practice and its role in the reduction of SSI and PJI rates have produced conflicting findings. To determine the utility of preoperative skin cleansing in preventing SSIs/PJIs, the effectiveness and logistics of the practice must be taken into account.

Preoperative skin cleansing can be executed using a variety of agents. Garibaldi et al. performed a prospective trial on over 700 patients and found rates of positive intraoperative wound cultures to be 4% for patients who showered and scrubbed with CHG, 9% for those who used povidone-iodine, and 14% for those who used medicated soap and water [3]. Several other published studies supported a connection between preoperative skin shower and CHG with decreasing overall culture rates [4–8].

Chlorhexidine bathing at home prior to surgery involves the use of either a 4% solution or a 2% cloth for a varying number of days based on the literature. Low-level evidence recommends the use of CHG cloths over bathing in its soap form [9]. Regardless of application methodology, CHG can either be bacteriostatic or bactericidal based on the concentration used for cleansing and its efficacy has been known to improve with frequency and duration of use [5,10,11]. The applicability of the aforementioned findings to SSI/PJI prevention in patients undergoing orthopaedic surgery remains unclear due to contradictory findings in the literature.

Kapadia et al. studied 3,717 patients who underwent primary or revision total knee arthroplasties. The group found that the use of a pre-admission chlorhexidine protocol was associated with a reduced relative risks of PJIs after total knee arthroplasty (TKA), when compared to patients who did not receive a CHG protocol (0.3% vs. 1.9%; rate ratio (RR): 6.3, 95% confidence interval (CI) 1.9 to 20.1, p = 0.002) [12]. Similar results were seen even when the two patient cohorts were risk-stratified. A review of modern papers from 2009 to 2015 also showed a reduction in infection rates with preoperative chlorhexidine preparation [13].

A systematic review by Webster et al. of over 10,000 patients in the Cochrane Database also concluded chlorhexidine washes were better than not bathing at all. However, the use of chlorhexidine washes did not seem to change infection rates [11]. Nevertheless, the review reported a lower relative risk for SSIs in patients who used CHG compared to those who used placebo (RR: 0.91, 95% CI 0.8 to 1.40). Farber et al. reported on over 3,700 total joint cases with 1,891 using 2% cloth wipes at the surgical site one hour prior to their procedure [12]. They also found no differences in infection rates at the one-year follow-up for either group.

As described above, the literature cannot affirm emphatically that skin cleansing at home prior to orthopaedic surgery has a role in reduction of subsequent SSIs or PJIs. There has yet to be any reports on the negative effects of preoperative skin cleansing at home prior to arthroplasty surgery and concerns for skin hypersensitivity associated with use of CHG are minor [4]. With really no downside and some potential upside (Table 1), it seems reasonable to consider some form of preoperative skin cleansing at home. Moreover, well-controlled trials are required to truly assess the efficacy of the preoperative skin baths. Initial cost data seems promising but may be institutionally-related with a potential net savings of $0.78 to $3.1 billion [14]. A true cost-assessment is necessary to understand if this low-risk means of infection prevention is cost-effective and whether it should be the standard of care prior to any orthopaedic/arthroplasty surgical procedure.

In conclusion, Table 1 summarizes studies that have been completed regarding chlorhexidine preoperative bathing and its effects on SSIs/PJIs. The heterogeneity of skin cleansing regimens and varying compliance rates make it difficult to isolate preoperative preparation as the main determinant for infection prevention in patients undergoing orthopaedic surgery. Despite the data listed, it is important to understand that compliance is always a concern with this protocol as one study found 78% noncompliance despite focused pre-surgery education efforts [15].

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TABLE 1. Studies related to preoperative skin cleansing protocols in TJA

Author	Number of Patients	Treatment	Outcomes	Level of Evidence
Webster [11]	10,157 all surgeries	Chlorhexidine, bar soap and no wash	No evidence that chlorhexidine was better	I
Farber [16]	3,715 TJAs THA—845 CHG; 815 no CHG TKA—1,046 CHG; 1,009 no CHG	2% chlorhexidine wipes	No reduction in infection at 1 year follow-up; 1.0% v. 1.3% infection overall; THA 1.2% v. 1.5%; TKA 0.8% v. 1.2%	III
Chlebicki [17]	17,932 all surgeries	Chlorhexidine, bar soap and no wash	No evidence that chlorhexidine was better	III
Eiselt [18]	1,463 TJAs	2% chlorhexidine wipes	50.2 % reduction in SSIs (3.19% down to 1.59%)	III
Johnson [19]	954 TJAs	2% chlorhexidine wipes	1.6% infection among noncompliant and 0% in the compliant cohort	III
Kapadia [12]	3,844 THAs; 998 with CHG and 2,846 without	2% chlorhexidine wipes	Decreased infection rate with CHG wipes; 0.6% v. 1.62%	III
Zywiel [20]	136/912 TKAs	2% chlorhexidine wipes	0% infection in CHG wipe group v. 3.0% in 711 other TKAs	III
Wang [21]	8,787 TKAs (2,615 CHG; 6,172 controls)	Variable	1.69% reduction in infection overall as well as in moderate and high risk patients	III
Cai [22]			6 studies reviewed and found a reduction in the risk of infection, revision surgery and length of stay	III
Kapadia [23]	564 TJAs (275 CHG and 279 Controls)	2% chlorhexidine wipes	CHG with 0.4% v. Controls with 2.9%; no adverse events—RCT	I
Kapadia [12]	3,717 primary or rev TKA (991 with CHG and 2,726 without)	2% chlorhexidine wipes	Risk reduction of infection from 0.3% compared to 1.9%, better reduction in medium risk compared to low risk	III

CHG, chlorhexidine gluconate; RCT, randomized control trial; THA, total hip arthroplasty; TJA, total joint arthroplasty; TKA, total knee arthroplasty

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QUESTION 2: Should skin and hair around a planned surgical incision be removed? If so, what is the best method and timing of removal?

RECOMMENDATION: Hair at the surgical incision site should be removed immediately prior to surgery using clippers or depilatory creams.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 84%, Disagree: 13%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Skin preparation prior to surgical incision has traditionally involved localized preoperative hair removal [1]. Despite a lack of statistical significances between the incidence of surgical site infections (SSIs) with and without hair removal, it is stll utilized during total joint arthroplasty (TJA) [1–3]. A recent meta-analysis conducted by Lefebvre et al. included findings from 19 randomized controlled trials (RCTs). Six trials included in the analysis compared shaving with no hair removal and results showed that no hair removal was associated with a lower risks of SSIs [3]. Another study compared chemical depilation with no depilation, and one study compared clipping with no depilation. In both cases, no significant differences were observed in paired analyses [3].

A 2006 Cochrane Systematic review of preoperative hair removal (updated in 2011) analyzed a total of nine RCTs, and found no significant differences in SSI rates among patients with or without hair removal at the incision site prior to surgery. It is worth noting, however, that investigators acknowledged that the comparison was underpowered [2,4]. Despite conflicting evidence on whether or not hair should be removed preoperatively, there is rationale behind the practice which should not be discounted. Depilation is thought to serve as a precautionary measure to reduce the risk of hair entering the open wound during the procedure. Potentially adverse outcomes due to hair contamination at the site of incision include foreign body tissue reactions subsequent to mechanical irritation during the wound healing process and infections [5].

Methods for depilation around a planned surgical incision include shaving, clipping and chemical removal. In 2011, Tanner et al. performed an update to a Cochrane Review previously published in 2006. A total of 11 randomized controlled trials related to hair removal prior to surgery were identified. The meta-analysis found electric clippers and depilatory creams to be associated with lower rates of SSIs in comparison to shaving with a razor blade [2]. These outcomes are attributed to the microtrauma inflicted on the skin during the shaving process, which then creates a nidus for bacterial colonizations and subsequent SSIs [6,7]. Chemical hair removal is a suitable alternative to clipping, however, there has been conflicting evidence on its efficacy. Lefebvre et al. showed that chemical depilation was associated with fewer SSIs compared to shaving. In the same study, indirect comparison with clipping as the reference showed no significant differences with chemical depilation [3]. Increased lengths of time to complete chemical depilation and the potential risk for chemical irritation of the skin make its utilization less advantageous [1–3,8]. In light of these findings, it is highly recommended that hair depilation be completed with an electric clipper [5,9]. Support for clipping has been reinforced by RCT results from Cruse and Foord, Alexander et al., Balthazar et al., Ko et al. and Taylor and Tanner [9–13].

In accordance with findings from the previous International Consensus Meeting, current literature lacks evidence to support an optimal time for hair removal [14]. Alexander et al. examined hair removal the night before and the morning of operations across a variety of surgical disciplines using both shaving and clipping. Excluding stitch abscesses, rates were lowest in the morning clipper group (at discharge: $x^2 = 4.894$, $p < .027$, at 30 days: $2 = 7.439$, $p < .006$) [9]. In an RCT of 798 patients undergoing spinal surgery, Celik and Kara found that shaving (with a razor) of the incision site, immediately before spinal surgery, may increase the rate of postoperative infections over not shaving at all [15]. According to a network meta-analysis of 19 randomized control trials conducted by Lefebvre et al., differences in outcomes based on timing of depilation were not statistically significant enough to conclude when hair should be removed prior to surgery [3]. If hair removal is to be done prior to surgery, it should be completed as close to the time of surgery as possible by either the surgical team or the trained nursing staff [1,3,6–9,14]. Though there is an overall lack of research specific to the environment in which preoperative hair removal should take place, it is recommended that it take place outside of the operating room, if practical [5,14,16].

Given what has been published to date, definitive evidence to dictate hair depilation practices with greater statistical significance is desired. Based on what has been established in the literature, it is recommended that hair be removed at the site of incision with depilatory creams or clipping shortly before the operation or outside of the operating room. This practice should be followed out of necessity and not routinely. If hair around the site of surgical incision does not interfere with the operation, it should not be removed due to the potential risks of skin and wound contamination.

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QUESTION 3: Does additional skin cleansing after placement of surgical drapes have a role in reducing the rate of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: Repeat skin cleansing following placement of surgical drapes may reduce bacterial colonization and the incidence of subsequent superficial SSIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 74%, Disagree: 15%, Abstain: 11% (Super Majority, Strong Consensus)

RATIONALE

The prevention of SSIs is a multifaceted effort. Among the many measures taken to reduce the incidences of SSIs, cleansing of the surgical site using a povidone-iodine or chlorhexidine solution prior to incision is considered a routine practice as this technique is thought to reduce the bacterial load at the surgical site [1–3]. Typically, the surgical site is draped after the cleansing solution has been applied. It has been hypothesized that bacteria may be reintroduced to the surgical site during this draping process [4]. There are a number of mechanisms through which this has been thought to occur, including lift-off of the draping, contamination of the surgical glove-tips, contact of the skin with non-sterile material and/or dropping of airborne particles from the room air onto the surgical site [5–7]. Thus, repeat skin cleansing following draping has been proposed as a way to prevent contamination of the surgical site before the procedure is initiated.

To our knowledge, there has been one prospective study assessing the efficacy of a second skin cleansing once surgical drapes have been applied. In a single-center randomized controlled trial, Morrison et al. compared two skin cleansing protocols in 600 patients undergoing total joint arthroplasty. The control arm consisted of a single cleansing, performed prior to the placement of surgical drapes, using a combination of 7.5% povidone iodine, 75% isopropyl alcohol and 10% iodine paint. The intervention arm consisted of a similar protocol, with a subsequent second skin cleansing with iodine and isopropyl alcohol, following the placement of surgical drapes. There were significantly lower rates of superficial SSIs in the intervention arm (6.5 vs.1.8%). However, no significant differences were noted in the incidence of overall SSIs (both superficial and deep) between the two cohorts [8].

In conclusion, and based on a single prospective study, it appears that skin cleansing following the application of surgical drapes may reduce bioburden at the skin and result in lower rates of subsequent superficial SSIs. However, there is a need for additional evidence to determine if a second skin cleansing after draping truly leads to lower rates of SSIs/PJIs.

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QUESTION 4: What pre-surgical skin preparation is most effective in reducing the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing orthopaedic procedures?

RECOMMENDATION: There appear to be no differences between various skin preparation agents (chlorhexidine gluconate (CHG) versus povidone iodine (PI)) as long as isopropyl alcohol is part of the preparation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 91%, Disagree: 6%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Skin preparation agents play an important role in reducing the risk of SSIs for patients undergoing surgical procedures. Organisms found in skin flora targeted by antiseptic solutions include staphylococci, diphtheroid organisms, *Pseudomonas* and *Propionibacterium* species, all of which can lead to harmful infections if they are allowed to multiply [1]. As recommended by the Centers for Disease Control and Prevention (CDC), counts of the aforementioned resident organisms and transient bacteria should be reduced on the surface of the skin by a bactericidal antiseptic prior to surgery [1]. The ideal skin preparation solution needs to work rapidly and also prevent the growth of pathogens for at least six hours after application [2]. Available skin prepping solutions used preoperatively to prevent SSIs include: iodine povacrylex and isopropyl alcohol, PI and CHG and isopropyl alcohol [3,4].

In a study of clean-contaminated upper gastrointestinal or hepatobiliary-pancreatic open surgery between 2011 and 2014, patients were randomly assigned to chlorhexidine gluconate or povidone-iodine, neither with alcohol. No differences were detected between chlorhexidine gluconate and povidone-iodine antiseptics for the prevention of SSIs [5]. Furthermore, Savage et al. found CHG to be an equally effective skin-preparation solution for lumbar spine surgery in comparison to PI [6].

Contrary to these findings, studies have found CHG to be a more superior agent to iodine povacrylex and isopropyl alcohol and/or PI. Saltzman et al. found CHG and isopropyl alcohol to be more effective than iodophor, isopropyl alcohol and PI in shoulder surgery cases [7]. Support for the use of CHG is evident a study done by Darouiche et al., which compared 2% CHG mixed with 70% isopropyl with 10% PI in clean contaminated wounds and found superiority of the former solution in reduction of SSIs [8]. A potential explanation for these results is that CHG has a high antibacterial activities, strong affinities for binding to the skin and prolonged residual effects [9]. It is important to note, however, that the CHG in the latter study was combined with alcohol, whereas, the PI was an aqueous solution. So effectively, the investigators compared two agents (alcohol plus CHG) against one.

In practice, CHG is more commonly delivered within an alcohol-based solution, as opposed to PI which is usually aqueous. Subsequently, there is debate as to whether or not the presence of alcohol in CHG has led to a bias in study results establishing its superiority over PI [10]. A previous study by Hakkarainen et al. did not find any unique effects of isopropyl alcohol, possibly nullifying this argument [11]. An ongoing cluster randomization trial in patients undergoing elective total hip arthroplasties (THAs) or total joint arthroplasties (TJAs) is being conducted to compare the efficacy of 0.5% CHG in 70% alcohol to that of 10% PI in 70% alcohol [12]. Results from this study may help clarify the role of alcohol in the efficacy of CHG and other skin prepping agents.

Further discrepancies in the selection of optimal skin-prepping solution can be found in a Cochrane review by Dumville et al. on skin antiseptics with a critical appraisal of the published articles on the issue of SSI [1]. This review demonstrated the following:

1. No statistically significant differences between skin preparation with PI and soap followed by methylated alcohol paint.
2. No differences between 7.5% aqueous povidone in 10% alcohol and CHG in 70% alcohol paint.
3. 0.5% chlorhexidine in methylated spirit had reduced risk of SSIs compared with PI in alcohol (one study only, with poor reporting of details).
4. No significant differences in number of SSIs when comparing aqueous and alcoholic solutions for skin preparations.

Given the conflicting findings from previously-mentioned studies as well as those conducted by Segal and Anderson, Pinhiero et al. and Swenson et al., an ideal solution of choice has yet to be identified for surgical site skin preparations [8,13]. Current literature lacks evidence to support the use of one solution over another in the prevention of SSIs, but there is an overall consensus that skin preparation solution should contain alcohol, originating from recommendations made by the CDC, International Consensus Meeting Group (ICG) and previously-published studies [2,3,5].

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QUESTION 5: Does surgical preparation of the skin on the whole limb instead of a partial limb reduce the rates of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: Surgical skin preparation of the whole limb may potentially reduce the risk of SSIs and/or PJIs by decreasing the risk of contamination associated with partial limb preparation. Despite the limited evidence, we recommend surgical skin preparation of the whole limb as there is a potential for contamination with partial limb skin preparation, and little downside to whole limb skin preparation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 84%, Disagree: 12%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

SSIs and PJIs can be devastating and costly complications associated with joint arthroplasty [1–3]. As multiple variables are associated SSIs and PJIs, considerable research has focused on reducing the rates of infections with the use of prophylactic antibiotics, utilization of laminar flow, various skin preparation solutions, medical optimization of patient risk factors, appropriate sterile techniques, etc.[4–9]. However there is a paucity of literature on partial versus whole limb skin preparation.

At the time of surgery, much effort is spent on sterile technique while prepping and draping the operative extremity to create a sterile surgical environment in an attempt to reduce the risks of SSIs and PJIs [10]. Often, surgical draping techniques are based on surgeon training and preferences rather than scientific evidences. Improper draping techniques may provide an opportunity for surgical field contamination [11]. One common extremity draping practice is to apply an impervious stockinette over a non-prepared foot rather than preparing the whole limb.

There are two potential sources of contamination associated with partial limb skin preparations: (1) potential bacterial contamination through the stockinette from strikethrough and (2) proximal bacterial migration from application of a sterile stockinette over a non-prepared foot.

Although the literature is limited, several small studies have evaluated partial versus whole limb skin preparation with conflicting conclusions. Bloome et al. assessed potential bacterial strikethrough utilizing an impervious stockinette over a non-prepped foot [12]. Of the twenty samples taken, only two grew one colony forming units of coagulase-negative *Staphylococcus*. Based on these findings, the authors concluded that strikethrough from a non-prepped foot is unlikely to be a significant source of contamination and therefore disinfecting the ipsilateral foot with a skin preparation solution is unnecessary.

Two other studies used either a fluorescent powder, or a non-pathogenic fluorescent *Escherichia coli* strain as a surrogate for contamination in order to evaluate proximal bacterial migration from application of a sterile stockinette over a non-prepped foot [13,14]. In both studies, the majority of extremities with a non-prepped foot had significant proximal migration of either fluorescent substance. The authors from both of these studies concluded that the application of a sterile stockinette over a non-prepped foot may be a source of proximal bacterial migration and, therefore, potential risk for surgical field contamination.

We propose that surgical preparations of the skin should include the whole limb given that the aim of this procedure is to reduce the microbial load on the patient's skin as much as possible. The prepared areas of the skin should extend to an area large enough to accommodate potential shifting of the drape fenestration, extension of the incision, potential for additional incisions as well as all potential drain sites. Despite our current knowledge about the antimicrobial activity of many antiseptic agents and application techniques, the best approach for surgical site preparation still remains unclear and further high-quality studies are warranted.

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QUESTION 6: Does surgical skin preparation starting from the surgical site, proximal portion of the extremity or distal portion of the extremity affect the rate of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: Despite the absence of supportive evidence, we recommend starting skin preparation from the site of surgical incision and moving towards the periphery. In general, skin preparation should be performed from a less-contaminated towards a more-contaminated area. In the case of a draining sinus, the area around the sinus should be prepped at the end of the preparation process.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 95%, Disagree: 3%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

Surgical skin preparation is one of the multiple steps implemented to minimize infections after surgical procedures [1]. Different techniques and antiseptic solutions are currently in use with proven efficacy for a number of agents. Skin preparation consists of application of an antiseptic solution to the surgical site and the surrounding areas. The most commonly-used antiseptics are alcohol-based solutions of chlorhexidine or povidone [2].

The process requires some mechanical effect (friction) for removing dead skin and bacteria from the surface of the surgical field, thereby reducing the number of viable bacteria.

Despite the lack of studies addressing the specific question cited above, reviews and guidelines are available recommending that skin preparation should start at the incision site and be directed towards the periphery [3–5]. In some guidelines/recommendations the use of concentric circles is recommended. It is commonly stated that the process should be directed from less to more contaminated areas, such as the foot, groin or the unsterile drape covering the tourniquet [4,6,7]. Including the entirety of the skin surface is important (for example, prepping the knee in full flexion and full extension can enhance the ability to obtain a thorough coverage of the intended sterile surgical surface areas) [8].

The amount of friction (force applied with the device soaked in antiseptic fluid against the skin), the number of applications over each area and direction are not specified in any guidelines or recommendations available to date. It is, however, known that sufficient time is required for an antiseptic solution to act on the surgical site allowing for maximum elimination of microorganisms [9]. Antiseptic agents have different action times and it is recommended that the manufacturer's instructions for each specific antiseptic be followed [10].

In the absence of specific studies addressing the above question, it is our recommendation that special attention be paid to preparation of the surgical site. The preparation should start from the surgical site, and then be directed to the periphery. It is also advisable to prevent the contact of the preparation sponge with more contaminated areas that could potentially transfer bacteria back to the surgical site.

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QUESTION 7: Does the type of surgical drape (disposable vs. non-disposable) used affect the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing orthopaedic surgery?

RECOMMENDATION: Unknown. The data from non-orthopaedic procedures suggests that disposable drapes resist bacterial passage and reduce the risk of subsequent SSIs. Impermeable barriers should be used regardless of whether disposable or non-disposable drapes are used.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 3%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Surgical drapes act as a barrier to prevent the contamination of the surgical field during a procedure. They are used to isolate the prepared surgical field from the non-sterile, non-surgical area. Reusable drapes are made of a woven material and are laundered and sterilized between procedures. In contrast, disposable drapes are usually made of non-woven material and are disposed of after each operation. Various physical properties of drapes and surgical conditions can affect the bacterial permeability of drapes. For example, it is known that there is increased bacterial passage when drapes are made wet by normal saline or blood [1,2]. Disposable drapes have been shown to decrease rates of bacterial passage, even when made wet by normal saline. However, this decreased bacterial transmission does not clearly indicate decreased risks of SSIs/PJIs [3,4].

We performed a systematic review using PubMed, Medline, Web of Science, Embase, Google Scholar and the Cochrane Library of studies in English. We included journal articles, communications and conference proceedings. Unfortunately, there is a paucity of studies relating specifically to orthopaedic surgery on this topic.

Randomized controlled trials in cardiac surgery and general surgery demonstrated no statistically significant differences in infection rates between the two types of drapes [5,6]. However, a different prospective randomized study of 102 reconstructive breast surgeries, demonstrated a statistically significant lower rate of infection 30 days after surgery in the disposable drape cohort (0 vs. 12%) [7]. The current literature on this topic is inconclusive and there are no studies involving orthopaedic or spine surgery patients. Future research efforts should be focused on this topic.

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QUESTION 8: Does the use of incise draping reduce the incidence of surgical site infections/periprosthetic joint infections (SSIs/PJIs)? Is there a difference in efficacy between incise drapes?

RECOMMENDATION: There is evidence to indicate that antimicrobial-impregnated incise drapes result in a reduction in bacterial colonization of the surgical site. While bacterial colonization of the incision may predispose to subsequent SSIs/PJIs, there is no literature to demonstrate that the use of incise drapes results in clinical differences in the rates of subsequent PJIs. Many surgeons prefer to utilize incise draping for physical isolation of sterile from non-sterile regions and to prevent migration of drapes during the procedure.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 89%, Disagree: 5%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Surgical incise draping, which is an adhesive material applied to the skin around the incision, is utilized by surgeons to potentially reduce the recolonization of the surgical site with host flora, which may predispose the patient to subsequent infections. It is important to distinguish between antibacterial-impregnated and non-impregnated drapes as the use of an antimicrobial agent in the drape may have a different influence on the rates of contamination of the incision and colonization. Unfortunately, the literature does not make such distinctions and the majority of the systematic reviews and even the guidelines by the World Health Organization (WHO) and

the Association of Perioperative Registered Nurses (AORN) have not made such distinctions. The adhesive barrier, usually containing an antibacterial material such as iodine, is applied prior to the incision and removed at the time of or after skin closure [1–3]. The rationale behind this practice is that the use of incise draping, in addition to conventional skin preparation, can reduce bacterial proliferation at the skin and serve as a physical barrier to block the translocation of recolonizing bacteria from the skin adjacent to the surgical site into the surgical field. This may then result in a decrease in the rates of subsequent SSIs/PJIs. However, it is important to note that using incise drapes as a substitutes for skin disinfection and preparation is not recommended [4].

Although many surgeons routinely utilize incise drapes, there is limited evidence to support that these drapes lead to a reduction in the incidence of PJIs or SSIs. Several associations do not support their routine use. The recent SSI prevention guidelines by WHO did not find any evidence to support the use of incise drapes during surgery and recommended against its use, however, none of the studies that formed the basis of such a recommendation were in orthopaedic surgery [5,6].

Several studies have demonstrated that impregnated incise drapes result in a reduction in bacterial colonization. Rezapoor et al. found that 12% of incisions with iodine-impregnated adhesive drapes and 27.4% without adhesive drapes were positive for bacterial colonization in a prospective randomized controlled trial of 101 hips undergoing hip preservation surgery [7]. Furthermore, patients without adhesive drapes were significantly more likely to have bacteria present at the incision at the time of skin closure and at all time-points of surgery. In addition, Fairclough et al. found that 122 hips undergoing acute hip fracture surgery, with iodophor-impregnated drapes placed 24 hours prior to the procedure, showed lower wound contamination rates from 15 to 1.6% compared to those without drapes [8]. In contrast, some studies have also found no differences in the rates of bacterial contamination with the use of adhesive drapes. Chiu et al. demonstrated no differences in wound contamination rates of 120 hip fracture patients when comparing plastic incise drapes with no drapes [9], while an randomized control trial (RCT) in cardiac surgery comparing use of drapes to no drapes showed earlier and more bacterial contamination following use of drapes [10].

While there is some evidence to suggest that bacterial contamination is reduced with impregnated incise drapes in non-orthopaedic surgery, there is no evidence to demonstrate that impregnated incise drapes result in a significant decrease in infection rates. This is likely because the majority of studies are underpowered given the relative rarity of PJIs or SSIs. In a recent Cochrane review of 3,082 patients, Webster et al. found that a higher proportion of patients developed surgical site infections with plastic drapes than patients in whom no drapes were used ($p = 0.03$) [1]. However, no difference was found when iodophor-impregnated drapes were used (1.03, 95% confidence interval (CI) 0.06 to 1.55, $p = 0.89$).

There is a need for studies evaluating the effect of iodine-impregnated incise drapes on infection rates in total hip arthroplasties and total knee arthroplasties as no clinical studies on this subject have been performed.

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QUESTION 9: Does the use of cloth or impervious stockinettes around the ankle and extremity affect the rate of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing orthopaedic procedures?

RECOMMENDATION: In the absence of evidence, we propose that a stockinette always be used to cover the unprepared skin in order to prevent potential contamination of the surgical field. Impervious stockinettes may be more resistant to soaking through during the surgery.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 89%, Disagree: 5%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Bacteria are thought to inoculate surgical wounds via an airborne pathway or through direct contamination by the patient's natural flora. Skin flora is a common source of infections, which are why appropriate antimicrobial skin preparations are of great importance

in the surgical theater. One common source of contamination is the foot. An impervious stockinette forms an impermeable barrier and is used to protect the surgical site from bacterial contamination. This is especially important because the feet are often held and handled by surgeons and assistants during hip and knee arthroplasty procedures.

Stockinettes are made of non-woven material and are designed for single usage. The efficacy of non-woven drapes in preventing contamination has been proven [1]. Stockinettes (cotton or impervious) are primarily designed to isolate foot microbes from the operative site, and additionally they provide circumferential coverage of the lower leg, including the popliteal fossa. There is no definite evidence in the form of a randomized controlled trial to suggest there are differences in deep or superficial infection rates with the use of a stockinette.

Another concern is whether the stockinette is used over a prepared or an unprepared foot. In 2012, Boekel et al. experimentally used fluorescent ultraviolet powder on volunteers and compared the contamination of the powder near the surgical site with below knee versus above knee application. The foot was not prepared and only the surgical site was disinfected. There was a significant proximal spread of the powder up to 71.8% proximally in the above knee application group. The most important conclusion from this study was that a stockinette should be used in conjunction with foot preparation [2].

This work was further tested by Marvil et al. in 2014, when non-pathogenic *E. coli* was applied to feet in cadavers and compared between the chlorhexidine prepared versus the unprepared foot with an impervious stockinette to mid-thigh level. Bacterial contamination at various sites including foot, ankle, 12 cm, 24 cm and 36 cm proximal to the ankle were assessed. In the non-prepared foot group, significant contaminations, as proximal as 24 cm to the ankle joint, were found, whereas no contaminations were found at any site in the prepared group. The merit of this study over the previous one was that the group used a non-pathogenic organism instead of a powder which may have had different adhesion characteristics [3].

In their recent review in 2016, Ratto et al. questioned the role of sterile stockinettes for the prevention of prosthetic joint infections [4]. The authors further highlighted the relevance of numerous preoperative, intraoperative and postoperative confounding factors that may have higher impact on causation of a deep infection. A 2014 study on glove contamination done by Makki et al. found that not a single incidence of glove contamination of the assistant who was holding the prepped foot with the stockinette occurred during prepping and draping [5]. Instead, the procedure of draping itself led to maximum incidences of contamination, especially with hip surgery. Thus, other aspects of draping could potentially be of more concern than the type of stockinette used with the antimicrobial prepared foot.

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1.10. PREVENTION: OPERATING ROOM, ANESTHESIA

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QUESTION 1: Does the type of anesthesia (general (GA) vs. neuraxial (NA)) influence the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: Compared to GA, NA appears to be associated with reduced risks of SSIs/PJIs after total hip arthroplasties (THAs) and total knee arthroplasties (TKAs).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 76%, Disagree: 12%, Abstain: 12% (Super Majority, Strong Consensus)

RATIONALE

Anesthetic technique may be a modifiable risk factor for the development of infectious complications after THA or TKA [1]. There are 16 observational studies [1–16] and 2 systematic reviews [17–18] comparing anesthetic type with risks of SSIs after joint arthroplasty.

Nine studies associated NA with reduced risks of SSIs after THA [2–3], TKA [4–6] or combined THA/TKA cohorts [1,7–9]. The earliest retrospective study of 3,081 patients from a national database in Taiwan described a protective benefit of NA [1]. Three large-scale reviews of The American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) concluded that GA was associated with more wound infections and more overall complications than NA [3–5]. Four additional large-scale studies sampled institutional [6], health system [7–8] or surveillance [9] databases and associated NA with lower incidences of post-arthroplasty SSIs. A large 30-year prospective study of SSIs after THA by a single surgeon found no overall influences of primary anesthetic choices on SSIs [10]. However, NA was associated with reduced risks of blood transfusions and avoiding transfusion reduced the incidence of SSIs.

Seven observational studies concluded that there is no influence of anesthetic type on the risks of SSIs after THAs [10–11], bilateral TKAs [12] or in combined THA/TKA cohorts [13–16]. However, two studies did find that NA was associated with decreased incidences of overall

systemic infections compared to GA (including SSIs, sepsis, urinary tract infections and pneumonia) [11–12]. One case-control study of primary and revision THAs/TKAs found no effects of anesthetic type on the development of SSI [14]. The remaining six population-based studies derived data from ACS-NSQIP [11], administrative [12,16], joint registries [15] or institutional databases [10,13] and found no associations between anesthesia type and SSIs.

There are two systematic reviews [17–18] (with one meta-analysis) [18] addressing this topic. Results were conflicting, with one systematic review/meta-analysis concluding that NA lowers the risk of post-arthroplasty SSIs [18] and the other failing to find any influences of anesthetic types on SSIs after total joint arthroplasties [17]. Notably, the latter systematic review included fewer than half the number of studies analyzed.

In summary, most of the available evidence investigating SSIs after joint arthroplasty is retrospective in nature or comprises prospectively collected data derived from large databases. Nevertheless, the overall study quality was moderate to high based on the individual study quality assessment. The evidence either (1) favors the use of NA, compared to GA or (2) shows no effect of anesthetic choice for reducing SSI risks after THAs/TKAs. Given that there is no evidence to support the use of GA to mitigate the risks of SSIs after joint arthroplasty and the preponderance of available data supports NA, we strongly recommend NA, when feasible, as the preferred anesthetic for THAs/TKAs.

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QUESTION 2: Can regional anesthesia be administered to patients with orthopaedic infections?

RECOMMENDATION: Yes. Central nervous system (CNS) infectious complications, such as meningitis, epidural abscesses or vertebral osteomyelitis are exceedingly rare when regional anesthesia is administered to patients with infections after an orthopaedic procedure. However, the potential benefits of neuraxial anesthesia likely outweigh any possible risks.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 91%, Disagree: 3%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

There are several proposed benefits of neuraxial anesthesia compared to general anesthesia for joint surgery, including fewer pulmonary and cardiac complications, surgical site infections and venous thromboembolic events as well as a reduction in mortality [1]. However, some surgeons and anesthesiologists alike consider the presence of an active infection to be a contraindication to administering neuraxial anesthesia due to the risks of seeding the spinal canal. This fear stems from case reports of patients developing devastating bacterial meningitis, epidural abscesses or vertebral osteomyelitis following spinal or epidural anesthesia [2,3]. In one historic study on military personnel from 1919, five out of six patients with bacteremia during a routine lumbar puncture subsequently developed meningitis [4]. Of 1,089 bacteremic patients, 2.1% of patients who received lumbar puncture and 0.8% of patients who did not receive lumbar puncture developed meningitis [5]. In a third study, 27% of children with pneumococcal sepsis who underwent lumbar puncture developed meningitis compared to 22% of children with pneumococcal sepsis who did not undergo lumbar puncture [6]. However, bacterial septicemia, in itself, is a risk factor for meningitis and it is likely that patients indicated for a lumbar puncture were those already at the greatest risk for developing meningitis. In patients without an active infectious source, the incidence of CNS infection has been reported to be as low as 0.04% [7–9].

Large studies on patients undergoing orthopaedic procedures for infections, who received spinal anesthesia, provide moderate to strong evidence of its safety. Of 474 patients undergoing removal of an infected prosthesis with neuraxial anesthesia, no patients developed epidural abscess or meningitis [10]. There was a single case of an epidural abscess and no cases of meningitis out of 764 operations performed for perioperative joint infections (PJIs) with neuraxial anesthesia [11].

There is additional evidence to consider outside of orthopaedics. In two retrospective reviews of 531 and 319 women with chorioamnionitis who received epidural or spinal anesthesia, there were no reports of epidural abscesses or meningitis [12,13]. Similarly, there were no infectious CNS complications in 46 children receiving epidurals for postoperative analgesia after thoracotomy for empyema [14].

While there are no randomized trials comparing the safety of neuraxial and general anesthesia for patients with joint infections, the preponderance of evidence suggests that infections related to orthopaedic procedures should not serve as a contraindication to the use of neuraxial anesthesia.

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QUESTION 3: Is it safe to use a neuraxial anesthesia (NA) in patients with active musculoskeletal infection?

RECOMMENDATION: Yes. The use of NA is safe in patients with periprosthetic joint infections (PJIs) without septicemia. There is limited evidence regarding the use of NA in patients with septicemia or other active musculoskeletal infections.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 3%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Orthopaedic surgery can be performed under general or neuraxial anesthesia (GA/NA). Besides the reduced requirements for sedatives and opioid analgesics, NA is associated with lower postoperative complication rates and shorter lengths-of-stay compared to GA after major lower limb surgery [1–4]. NA also decreases the incidences of postoperative surgical site infections (SSIs) following total joint arthroplasty (TJA), by decreasing operative time, improving tissue oxygenation and offering a better ability to maintain normothermia [5].

In spite of its numerous benefits, NA can have severe infectious, vascular and neurological complications, though the rates of such complications are extremely low. Infectious complications may result in devastating morbidity and mortality, such as abscess, meningitis, paralysis or death [6]. Incidences of infectious complications after NA have been reported to be between 0.05 and 0.001% [6]. Pumberger et al. analyzed more than 100,000 consecutive TJA cases utilizing NA and found epidural hematoma in only eight patients, reflecting an incidence of 0.007 % [7].

One of the risk factors for meningitis and epidural abscess, following epidural or spinal block, could be pre-existing sepsis or bacteremia [8–10]. In a recent retrospective study of 101 spinal epidural abscesses, bacteremia was the most commonly identified cause (26%) [11]. A 2017 Practice Advisory by the American Society of Anesthesiologists Task Force reported that NA is only relatively contraindicated in the presence of bacteremia and that the evolving medical status of the patient should also be taken into account. The decision to perform a neuraxial technique should be determined individually and prophylactic antibiotic therapies should be considered prior to the procedure [8].

The safety of spinal and epidural anesthesia in patients presenting with localized infections has been demonstrated in the literature [12–16]. Goodman et al. studied the safety of NA in 531 patients with chorioamnionitis. None of the patients developed an infectious complication [12]. Regarding spinal infections and NA, patient-controlled epidural analgesia may be administered in patients with surgically treated spondylodiscitis as evidenced by the study performed by Gessler et al. [16].

To our knowledge, there are only two original papers directly related to the question of whether NA is safe in patients with active musculoskeletal infections [13,15]. Gritsenko et al. retrospectively

evaluated 474 patients who underwent removal of an infected TJA after receiving NA [13]. In this cohort, 4.2 % had bacteremia and 88% had positive intraoperative joint cultures. None of the patients developed meningitis or epidural abscesses but one patient developed a psoas abscess. The authors recommended that no epidural catheters remain in place after the surgical procedure. Rasouli et al. studied 539 patients who underwent revision TJA due to PJIs [15]. A total of 134 patients received NA, 143 received GA and 260 received combined GA and NA. There were no cases of meningitis but one patient developed an epidural abscess after NA. It is important to note that this patient had 6 revision surgeries during a 42-day period, 2 under NA and 4 under GA. Additionally, the diagnosis of an epidural abscess was made 36 days after the last procedure. The abscess was drained and the patient was discharged in good condition. The authors concluded that the incidence of central nervous system infection after NA for PJIs is extremely rare and NA can be considered safe during surgery for PJIs [15].

According to the studies by Gritsenko et al. and Rasouli et al., NA can be considered a safe option during PJI revision surgeries [13,15]. Extrapolating the results from PJI [13,15], spine [16] and obstetric [12] literature, NA may be safe in other cases of active musculoskeletal infection, but there is insufficient evidence for this particular question. The decision of which anesthetic technique to use with active musculoskeletal infections should be determined individually given the current status and co-morbidities of the patient. Additionally, caution should be utilized particularly in patients with septicemia. The numerous benefits of NA must also be considered in this decision-making process.

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1.11. PREVENTION: OPERATING ROOM, PERSONNEL

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QUESTION 1: Does the number of individuals in the operating room (OR) affect the rate of surgical site infection/periprosthetic joint infection (SSI/PJI)? If so, what strategies should be implemented to reduce traffic in the OR?

RECOMMENDATION: Yes. The number of individuals in the OR and door openings (DO) during total joint arthroplasty (TJA) are correlated to the number of airborne particles in the OR. Elevated airborne particles in the OR can predispose to subsequent PJIs. Therefore, OR traffic should be kept to a minimum. Multiple strategies, outlined below, should be implemented to reduce traffic in the OR during orthopaedic procedures.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 98%, Disagree: 2%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The number of persons and DOs in the OR have been reported to disrupt the airflow [1–4], and therefore affect the quality of air in the OR. No high-level evidence study exists, though, to directly link the OR traffic with the development of PJIs. The multivariate nature of PJIs as well as its low incidence require an enormous study population to directly evaluate the influence of OR traffic on PJIs, which is technically difficult.

There is no consensus on the best methods of monitoring air quality in the OR [5–9] . Though particle counting is less demanding and more standardized than microbiological sampling, the information obtained is indirect. Furthermore, the air particle counts cannot accurately predict the microbial contamination of the OR air [10].

The number of personnel in the OR and number of DOs have been recognized as a major source of increased number of particles

in the OR air [5,11,12]. Several observational studies have demonstrated a positive relationship between the number of individuals and DOs and the number of aerosolized particles in the OR [3,11,13,14]. Ritter et al. [15] reported that the bacterial counts were 34-fold higher when 5 or more persons were present, compared to an empty OR.

DOs may lead to increased contamination rates by two mechanisms. First, DOs in the OR are linked to the number of staff in the OR during operations [16]. Second, DOs create turbulence between two spaces and disrupt the positive laminar flow of the OR which might subsequently lead to faster spread of airborne bacteria and particles to the surgical field [1,13,17,18]. Andersson et al. [14] showed a positive correlation between traffic flow rates and air bacterial counts in orthopaedic procedures. They also identified a direct correlation between the number of people present in the OR and bacterial counts. Quraishi et al. [19] demonstrated a direct correlation between the activity level of OR personnel and bacterial fallout into the sterile field. Additionally, Lynch et al. [20] showed an exponential relationship between the number of DOs and the number of personnel in the OR. In their series, an information request was the main reason for the majority of DOs.

Several studies have evaluated the incidences and causes of DOs during elective TJAs [8,18,20–22]. Rates of 0.19/min to 0.65/min DOs for primary and 0.84/min for revision TJAs have been reported [3,18,20,21]. The highest percentage of DOs occur during the pre-incision [18] or post-incision periods [10]. The majority of the traffic constitutes of the circulating nurses, followed by surgical implant representatives and then the anesthesia and orthopaedic staff [18,20,21]. The most frequently-reported single reason for DOs is getting supplies along with gathering and transferring information. Scrubbing in and out during the procedure, staff rotation for breaks, talking with colleagues in the corridor, coordinating with nursing and anesthesia personnel were also reported as reasons for DOs [18,21]. It is important to note that the rate of unjustified traffic was considerably high among different studies [8,18].

Experimental, observational and simulation studies have evaluated the influence of OR traffic on the OR environment [4,13,23–26]. Mears et al. [23] identified that DOs in 77 of 191 TJAs overwhelmed the positive OR pressure, allowing airflow to reverse from the hallway into the OR. The loss of positive OR pressure was a transient phenomenon, however the time needed for the recovery of pressurization was unknown. On the contrary, Weiser et al. [4] reported that positive pressure was not defeated during any single DO, however they found that contaminated outside air entered the OR if two doors were simultaneously opened. In their study, OR pressure recovery took approximately 15 seconds following a DO. They supported that OR contamination was more likely attributable to the effects of the personnel who enter the OR rather than as a primary cause of DOs. Furthermore, Rezapoor et al. [25] demonstrated that the laminar airflow was protective against the negative influences of the number of people and partially of DOs. Smith et al. [13] also showed that bacteria colony forming units cultured on plates placed in sterile basins in the OR during the operation were significantly negatively associated with any DOs and the function of laminar air flow.

An increased trend of PJIs is associated with high OR traffic [2,11,17,27]. Pryor et al. [27] demonstrated a positive, but non-significant, correlation between the total number of people who enter the OR and infection rates. In a cohort of 2,864 operated patients, the infection rate was 1.52% when fewer than 9 and 6.27% when more than 17 different people entered the OR. Cross-sectional observational studies evaluated the effects of measures to control OR traffic and the number of personnel as a preventative strategy in reducing PJIs [1,8,18,28]. Knobben et al. [28] observed that systemic and behavioral measures in the OR, including limiting unnecessary activity and individuals in the OR, can lead to a significant reduction in the incidence of prolonged wound discharges and superficial PJIs as well as a non-significant decrease in the deep PJIs. It was, however, difficult to determine the influence of each measure on the final results.

Numerous strategies have been proposed to reduce OR traffic and subsequent contamination of the OR environment. These include: (1) Limitation of the number of persons who are present during orthopaedic procedures - observers, residents, researchers and external vendors should be kept to a minimum [3,18]; (2) Storage of the frequently used instruments in the OR; (3) Proper education of OR personnel regarding the potential correlations between OR traffic and infections [4,13,18,20]; (4) Careful preoperative planning and templating so as to have all necessary supplies and implants in the OR [18,26]; (5) Reduction of the OR traffic using verbal interventions to the staff [1]; (6) Lockage of the external door immediately after the entry of the patient into the OR with entrance only through the inner doors [4,13,21]; (7) Minimization of the staff rotation during each TJA ideally to zero [21]; (8) Use of the intercom for communication with the outer door [3]; (9) No door openings for social visits, clinical discussion or anesthetic supplies for the next case; (10) Use of a door alarm to decrease DOs [29]; (11) Prohibition of staff to enter or leave the OR unnecessarily and (12) Opening the necessary equipment as close as possible to the time of incision in order to reduce the exposure of the sterile instruments to the increased traffic [18].

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QUESTION 2: Does the risk of surgical site infection/periprosthetic joint infection (SSI/PJI) increase when the surgeon performing the arthroplasty procedure has an upper respiratory infection?

RECOMMENDATION: It is unlikely that the risk of SSIs/PJIs is increased in patients undergoing orthopaedic procedures when the surgeon or surgical team has an upper respiratory infection.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 85%, Disagree: 8%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Reports of the transmission of hepatitis B virus (HBV), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) from healthcare workers to patients during invasive procedures have raised the question of whether physicians infected with upper airways pathologies should perform invasive orthopaedic procedures such as joint arthroplasty. [1,2]. It has been previously suggested that surgeons affected by HBV, HCV and/or HIV should not (strong recommendation: against) perform major joint arthroplasty surgery (e.g., hip, knee, shoulder and elbow), open spine surgery and/or open pelvic surgeries because of the very high risk of disease transmission to patients [3]. However, very little is known on the risks of potentially increased SSIs/PJIs when the surgeon performing the arthroplasty has an upper respiratory infection. On the other hand, Navalkele et al. demonstrated that surgical site infections were more likely to develop in patients who had respiratory tract infections within 30 days prior to surgery (20 vs.6.6%, odds ratio (OR): 3.42; 95% confidence interval (CI) 1.62 to 7.22, p =.0034) [4].

Surgical site contamination by airborne particles is ascribable in some cases to direct settling of the particles on the wound. Condensation droplets measuring less than 5 µm, produced with coughing and sneezing are able to contaminate the surgical site if the surgeon is not isolated by a helmet sealed within a gown [5]. If the principal pathogens responsible for common cold, rhinitis and influenza (rhinovirus, coronavirus, parainfluenza virus, influenza virus, respiratory syncytial virus) are generally not responsible for SSIs, other microorganisms are commonly associated with a viral respiratory disease. *Staphylococcus aureus,* coagulase-negative *Staphylococcus, Streptococcus*, gram-negative bacteria and methicillin-resistant *S. aureus* (MRSA) (measuring 0.2 – 5 µm) can adhere to the condensation droplets to form colony-forming units (CFUs), and be infectious in short-range scenarios (less than 1 meter), theoretically leading to SSIs. Operating room counts lower than 10 CFUs are mandatory for knee and hip arthroplasty [6].

A sneeze can generate up to 40,000 droplets, [7] which can evaporate to produce droplets of 0.5 to 12 µm, while a cough can generate about 3,000 droplet nuclei, the same number as talking for 5 minutes [8].

Despite all these potential risks, there is strong evidence that personal protective equipments (PPEs) including gowns, facemasks and gloves, in addition to the usual contact–transmission prevention precautions (i.e., hand washing, avoiding touching mucous membranes of the eyes, nose and mouth), are effective in reducing surgeon-to-patient disease transmissions [9,10]. Additionally, many environmental factors controllable in a standard OR (i.e., temperature, humidity, air flow and ultraviolet radiation) affect the viability of an infectious agent further reducing the risks of disease transmissions and PJIs afterwards [11–14].

As a result, we conclude that the widespread use of PPEs, in addition to the usual contact-transmission prevention precautions, protect the susceptible patient from disease transmission and PJI development. However, the lack of high-level evidence results in a moderate level of strength for this recommendation.

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QUESTION 3: Does the technique, duration or agent used for surgical hand scrubbing by the surgeon and operating room personnel alter the patient's risk of surgical site infections/ periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: Unknown. Surgical hand preparation should be performed either by traditional scrubbing with a suitable antimicrobial soap and water or by using a suitable alcohol-based hand cleansing agent.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 5%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Multiple reviews have been performed in order to study this matter, however none of these reviews have been able to show differences between different surgical hand antisepsis on SSIs rates. There is indicative evidence advocating alcohol-based hand rubs (ABHRs), which reduce colony forming units (CFUs) in hands better than traditional scrubbing as well as cause less skin damage in comparison [1–7].

A Cochrane database review was published in 2016 assessing the effect of different surgical hand antisepsis on preventing SSIs. They compared the effects of different techniques (i.e., hand rubbing vs. hand scrubbing), products (i.e., different formulations of ABHRs vs. plain soap vs. medicated soap) and application times for the same product. The conclusion was that there is no firm evidence that one type of hand antisepsis is better than another in reducing SSIs [2].

The review concludes that there is evidence that the ability of different hand antisepsis to reduce CFUs is different but the clinical outcomes of these findings are unclear. Chlorhexidine gluconate (CHG) scrubs may reduce the number of CFUs on hands compared with povidone iodine (PVPI) scrubs. Alcohol rubs with additional antiseptic ingredients may reduce CFUs compared with aqueous scrubs [2].

This review also evaluated the duration of hand antisepsis, and concluded that a three-minute scrub reduced CFUs on the hand compared with a two-minute scrub but this was very low-quality evidence. Furthermore, findings about a longer initial scrub and subsequent scrub durations are not consistent. It is also unclear whether nail picks and brushes have an impact on the number of CFUs remaining on the hand. The Cochrane review states that almost all evidence available to make decisions about hand antisepsis were informed by low or very low-quality evidence [2].

The World Health Organization's recommendations on preoperative measures for SSI prevention published in 2016 state that the overall evidence (rated as moderate quality) showed no differences between ABHR and hand scrubbing in reducing SSIs. They also concluded that studies using CFUs on participants' hands as the outcome showed that some ABHRs are more effective than scrubbing with water and antiseptic or plain soap. However, the relevance of this outcome to the risks of SSIs is uncertain [1].

Oriel et al. published a study in 2017 in which the authors reported the incidence of SSIs after introducing ABHR as an alternative to traditional aqueous surgical scrubs. The SSI rates for traditional scrubbing ($n = 4,051$), and ABHR ($n = 2,293$) were similar (1.8 vs. 1.5%, $p = 0.31$) [6,7].

Also, in 2016, Oriel and Itani found that none of the SSI studies have shown any benefit of one product type over another, even though the literature shows the inferiority of PVPI to both CHG and ethyl alcohol (EA). EA often outranks CHG in non-clinical in vivo tests. Both ABHRs and CHG are preferred to PVPI for surgical hand antisepsis [3].

In 2015, Shen et al. performed a study to compare a conventional surgical scrub with an ABHR in order to evaluate antimicrobial efficacy. They performed hand sampling for cultures before and after operations. The culture positive rates of ABHR were 6.2% before operations and 10.8% after operations. Both rates were lower than the conventional surgical scrub (47.6% before operations [$p < 0.001$], and 25.4% after operations [$p = 0.03$]). Multivariate analysis showed that ABHR was a significant protective factor for positive hand cultures [5].

Liu et al. published a review in 2016 in which the authors studied the influences of different hand antisepsis on SSI rates and

skin integrity. They advocate ABHR because it appears to cause less skin damage than traditional scrub protocols but is as effective as traditional scrub. Some studies have demonstrated relatively poor compliance for optimal scrubbing time and techniques by personnel using a brush with personnel preferring to use AHBRs [4].

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QUESTION 4: Does the type of cap worn by the operating room (OR) personnel matter?

RECOMMENDATION: Unknown. The evidence would suggest that, since normal hygiene such as daily shampooing and showering does not result in bacterial decontamination of OR personnel, some form of disposable head covering is prudent. Whether this takes the form of a bonnet, bouffant or helmet is unknown. We recommend that the cap should cover the entire scalp, ears and facial hair.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Human hair serves as a reservoir for bacteria shedding and as a potential source of contamination in the operating theater [1]. Summers et al. cultured bacteria from the hair of inpatients, hospital staff and outpatients and compared them with nasal carriage, finding that *Staphylococcus aureus* colonization was even more common in scalp hair than in the nares [1]. It is critical to determine the most appropriate surgical cap for limiting bacterial spread and desquamation from the skin/hair of OR personnel in order to minimize potential contamination, even with most modern ventilation systems [2].

A study in 1991 recommended the discontinuation of headwear in OR staff, and determined that adequate ventilation and laminar flow was enough to combat microbial sheddings, as the authors did not find significant reductions in microbial air counts with use of head covers [3]. However, conflicting evidence arose when a study by Fridberg et al. [4] demonstrated that airborne contaminants were three to five times ($p < 0.001$) greater compared to the absence of headwear. Additionally, they found that wound contamination without the use of headwear increased by 60-fold in comparison to wearing head covers. The authors concluded that laminar flow units should be held in question with regard to replacing the use of head covers and in the risk of surgical surface contamination.

At present time, there are few studies published within the past decade comparing different types of caps, their effects on OR environment bacterial counts and surgical site sterility. A recent study by Markel et al. [5] investigated the degree of airborne contaminates with different head covers (disposable skull caps, disposable bouffant hats and cloth skull caps) in the OR during standardized mock surgical procedures. They measured the number of particulates being 0.5-µm and 1.0-µm in size and found that there were significantly higher numbers of airborne particulates when disposable bouffant hats were used compared to cloth surgical caps ($p < 0.05$). There was no significant differences seen in airborne particulates after active sampling when comparing bouffant hats with disposable surgical hats. However, for passive settle plate analysis, it was determined that bouffant style hats allowed for a significantly greater amount of microbial shedding at the sterile field compared to disposable skull caps ($p < 0.05$). They further concluded that disposable bouffant hats had a higher permeability/porosity and yielded higher levels of bacterial shedding in the OR. They endorsed the use of skull caps for reducing the potential risk of contamination from scalp hair. This, however, is against the recommendation of the Association of Perioperative Registered nurses for OR personnel to wear bouffant caps. It should be considered that the outcome studied was contamination in vitro in comparison to actual surgical site infections (SSIs) seen in surgical patients [6].

More recently, a study by Kothari et al. [7] revealed that SSI rates were not significantly different ($p = 0.016$) in surgical cases where attending surgeons wore bouffant hats (8%) versus in those where surgeons wore surgical skull caps (5%). The authors analyzed data from a previous prospective randomized trial on SSIs in accordance with hair clippings in a multitude of surgical specialties and in more than 1,500 patients. These findings are in contrast to the findings of the studies by Markel et al. [6] and Kothari et al. [7], which advocated for operating room staff to choose OR head attire based on preference as the choice in OR headwear did not play a role in the development of both superficial and deep SSIs [5,7].

It can be concluded that with a scarcity of recent literature addressing the use of different surgical caps on the impact of bacterial shedding/air borne particulates and the potential for SSIs in the OR, it is recommended that further research is needed to substantiate the claims made regarding OR headwear. Clearly, a randomized trial of coverage versus none would be unethical to conduct. There is ample evidence, however, to suggest that gram-positive bacteria are often carried on the facial skin, hair and ears of hospital personnel.

Several case studies report on outbreaks of SSIs with unique bacterial strains associated with carriage by identified surgical team members.

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QUESTION 5: Should surgeons and operating room (OR) personnel wear a mask and a cap in the OR?

RECOMMENDATION: Yes. The use of surgical facemasks (SFMs) and caps by staff in the OR is presumed to reduce the frequency of surgical site infections (SSIs). There is a paucity of data with few studies addressing this topic. The long-standing established standard of SFMs and caps in the OR should continue despite the lack of strong evidence demonstrating clinical efficacy and a lack of persuasive evidence for altering current clinical practice. Evidence for the potential role for SFMs in protecting staff from infectious material encountered in the OR is also controversial. In the absence of convincing clinical evidence either for or against wearing masks and caps in the OR, it is advisable, at this time, to continue to follow local or national health and safety regulations.

LEVEL OF EVIDENCE: Limited. Conflicting study results are published. Further research is likely to have an important effect on our confidence in the response and may change this recommendation. The evidence is currently supported only by observational studies, with no randomized control trials or other high level studies available.

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Surgeons and nurses typically wear disposable facemasks and caps in the OR. The purpose of face masks is thought to be two-fold: (1) to prevent the passage of bacteria from the surgeon's nose and mouth into the patient's wound and (2) to protect the surgeon's face from sprays and splashes from the patient. Facemasks are thought to make wound infections after surgery less likely. However, incorrectly-worn masks may paradoxically increase the likelihood of the wound becoming contaminated with shed skin and debris. It is unclear if by wearing facemasks the surgical team increases or decreases the risk of SSIs in patients undergoing clean surgeries including elective joint arthroplasties [1].

Infections occurring in a wound created by an invasive surgical procedure are referred to as SSIs. Postoperative wound infections increase the lengths-of-hospitalization, and predictably, substantially raise the costs of care. SSIs account for a marked fraction of health care associated infections, and can be associated with considerable morbidity, with estimates that over one-third of postoperative deaths are at least partly attributable to SSIs. In the OR there are, therefore, many procedures and practices in place intended to reduce the probability of infectious material transfer between OR staff and patients [2].

SFMs provide a physical barrier between bacteria of oropharyngeal and nasopharyngeal origin and an open wound. Additionally, SFMs potentially protect OR staff by providing a physical barrier to infectious bodily fluid splashes from the patient. Wearing a SFMs in the OR is one of many long-standing preventative practices, yet controversy still exists as to the clinical effectiveness of SFMs in reducing the frequency of SSIs. General-purpose disposable SFMs, however, are not specifically designed to protect the wearer from airborne infectious particulates [3].

The 1999 Centers for Disease Control and Prevention's (CDC) "Guideline for Prevention of Surgical Site Infection" [4] strongly recommended the use of SFMs for prevention of SSIs. The 2007 CDC "Guideline for Isolation Protection" [5] reiterated the recommended use of different qualities of SFMs for sterile procedures without adding any new scientific data in support of this recommendation. Most international guidelines acknowledge the controversy surrounding the use of disposable SFMs [6,7] with no clear clinical or experimental evidence that wearing SFMs effectively diminishes the incidence of SSIs. The incidence of SSI is itself dependent upon multiple other variables, particularly the patient's immunological status, and the behavior of the surgical team in and around the operative field.

The systematic review by Lipp and Edwards [8] included 2,106 patients undergoing elective clean surgeries. Clean surgery is defined as surgery where no inflammation is encountered and the alimentary, respiratory and genitourinary tracts are not entered. The conclusion from the study was unclear whether the wearing of SFMs by the surgical team increased or decreased the risks of SSIs. The systematic review by Bahli [9] included data on 8,311 patients undergoing elective surgeries and concluded that the evidence regarding the efficacy of SFMs in preventing postoperative wound infections in elective surgery is inconclusive. At this time, therefore, it is still difficult to recommend changing the established clinical practices of wearing facemasks in rooms on the basis of current evidence.

The topic of OR headgear has been very controversial and the quality of data used to support OR policy surrounding this topic is marginal. A 1991 study by Humphries et al. suggested that wearing any type of headgear in the OR did not decrease bacterial counts. However, the use of proper ventilation techniques drastically reduced these counts and the authors concluded that non-scrubbed individuals did not need to wear headgear because proper ventilation likely counteracted any bacterial shedding [10]. Ten years later, however, a conflicting study by Friberg et al. demonstrated a two-to-five-fold increase in bacterial contamination at random sites throughout the OR when headgear was not worn and a 60-fold increase in contamination in the wound bed [11]. Considering these results, it is apparent that wearing headgear markedly decreases the probability of spreading fomites and debris to an open surgical wound. However, it remains uncertain whether this translates into a greater risk of SSIs and periprosthetic joint infections as no study specifically examining this possibility has ever been conducted.

Humphreys et al. performed air cultures in a sealed OR when volunteers wore either surgical hoods or no head coverings. The investigators found little effects of a head cover on volumetric air sampling cultures (i.e., no settle plates were used to simulate settling of bacteria near an OR bed). Nevertheless, the investigators concluded that personnel assisting in the surgical procedure should continue to wear head coverings [10]. Markel et al. [12] observed that disposable bouffant style hats had high permeability, greater particle penetration and increased porosity, leading to higher levels of bacterial and particulate contamination in a dynamic OR environment. When compared with disposable skullcaps, bouffant hats cannot be considered superior. Furthermore, if properly laundered, the use of cloth skullcaps may yield better sterility compared with standard disposable bouffant hats.

The use of SFMs and caps by staff in the OR is presumed to reduce the frequency of SSIs. Although there is a paucity of solid data on this topic, there is no persuasive evidence to indicate any rationale for altering clinical practices. The long-standing practice of wearing SFMs and caps in the OR should continue despite the lack of strong clinical evidence supporting their use. Evidence supporting the potential role for SFMs in protecting staff from infectious material encountered in the OR is also controversial. In the absence of strong clinical evidence for or against wearing masks and caps in OR, it is advisable at this time to continue to follow local or national health and safety regulations.

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QUESTION 6: Does the presence of exposed facial hair (beard and mustache) on any operating room (OR) staff or surgeon influence the rate of surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing orthopaedic procedures?

RECOMMENDATION: Although facial hair may increase the risk of bacterial contamination under certain circumstances, risks should ideally be assessed in the context of masking, with and without nonsterile hoods, where limited and contradictory data exists.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 89%, Disagree: 5%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Facial hair has the potential to harbor pathogenic bacteria and even with routine hygiene, bacterial shedding from these sources may lead to contamination resulting in infection during surgical procedures. At any given moment, the inner surface of an OR staff's surgical mask contains up to 100 times the amount of bacteria that is present on the OR floor [1]. However, even after the strict advent of OR policies mandating the coverage of exposed head and facial hair, there has been little to no evidence of decreased SSIs [2]. For surgeons and scrubbed personnel, it remains a controversial topic whether beards and exposed facial hair predispose patients to increased risks

of infections in the OR [3]. A study examining the relative contamination of air in ORs showed that of those who were dispersers of *Staphylococcus aureus* (4%, n = 3,039), 15.5% of these subjects had *Staphylococcus aureus* colonizing in their beards [4].

A study by Parry et al. investigated aerobic bacterial shedding in 10 bearded men, 10 clean-shaven men and 10 women by measuring colony forming units (CFUs), after having each cohort make standardized facial motions above agar plates while unmasked, masked and in surgical hoods [5]. They found the CFUs and bacterial shedding in the bearded group was no greater in comparison to the clean-shaven group when masked (1.6 vs. 1.2 CFUs, p = 0.9), unmasked (9.5 vs. 3.3 CFUs, p = 0.1) or in surgical hoods (0.9 vs. 1.3 CFUs, p = 0.6). Additionally, they found that surgical hood use did not decrease the total number of bacteria isolated per subject with a mean of 1.1 CFUs while hooded vs. 1.4 CFUs with the mask alone (p = 0.5). Unmasked subjects shed a mean of 6.5 CFUs more than the number shed while masked (p = 0.02) or hooded (p = 0.01). The authors also found that when participants were stratified by beard length, those with beards 20 mm or longer shed more than clean-shaven subjects when unmasked (18 vs. 3.3 CFUs, p = 0.03), but this difference was eliminated with the addition of a mask. The authors concluded that beards in an operative environment appear to add no definitive risks of bacterial shedding in comparison to those who do not have facial hair, when proper facial coverings are utilized.

Conversely, a study by McLure et al. found that bearded males shed significantly more bacteria than clean-shaven males (p = 0.01) or females (p = 0.01) at rest with masks [6]. They also examined the effects of dermabrasion due to mask adjustments and wiggling on the shedding of bacteria in those with and without facial hair in a study of 10 bearded men, 10 clean-shaven men and 10 women all who wore masks above agar plates. The authors recommended avoidance of behaviors that encourage unnecessary face mask movement and concluded that it may be advisable to remove facial hair in an operative environment due to the potential risk of bacterial shedding.

As an alternative to facial hair removal, nonsterile surgical hoods used alongside face masks may be considered. In a study examining the air-borne transmission of bacteria and particles during standardized sham operations (n = 30), there was up to a 60-fold increase in bacterial sedimentation rate (p < 0.01) found in surgical wounds when no head covers (disposable hood/triple laminar face mask or sterilized helmet aspiratory system) were worn [7]. Thus, irrespective of whether facial hair is present or not, it may be necessary under specific circumstances to have some form of headwear during surgical procedures for scrubbed personnel.

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QUESTION 7: Does strict adherence to not wearing operating room (OR) attire outside the hospital or outside the restricted OR area reduce the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: We recommend that OR personnel wearing attire that has come into contact with areas outside the restricted OR environment not wear the same attire during elective arthroplasty or complex orthopaedic procedures.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 90%, Disagree: 8%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

The use of standardized OR attire has been implemented to help reduce the shedding and desquamation of human cells and bacteria from the skin of personnel in restrictive hospital environments [1–3]. Specific institutions have further aimed to reduce contamination by requiring the use of covers and gowns over scrubs when leaving restrictive hospital environments, such as the OR [1–3].

Various institutions utilize these protocols to date, even in light of the deficient data on whether OR attire worn outside restricted hospital environments plays a role in the development of SSIs and/or PJIs. A report from the Hospital Infection Society Working Group in 2002 examined the ritualistic behaviors and numerous studies regarding the methods of sterility in the OR [4]. They determined there to be little to no concrete evidence showing that wearing OR attire in external unrestricted hospital environments and returning without changing led to an increase in SSIs and the rates of wound infections [4].

There have been some studies examining how surgical attire and hospital scrubs collect contaminants upon travel outside the

hospital and restricted OR areas. A prospective cross-over study performed by Hee et al. examined fabric samples from the scrubs of 16 anesthesiologists divided into 3 cohorts that had worn their scrubs in different environments (Group 1: OR only, Group 2: OR and hospital wards, Group 3: OR, hospital wards and outpatient offices) in an effort to determine the level of contamination to attire as result of different environmental factors [5].

Fabric samples were collected for microbiological analysis from the chest, waist and hip of each anesthetist every 150 minutes over the course of an 8-hour work day. The group determined there to be no significant differences in the bacterial colony counts among the 3 cohorts in comparing the bacterial colony-forming units (CFUs) ($p = 0.669$ for Group 1: 16.8 CFU vs. Group 2: 15.3 CFU; $p = 0.942$ for Group 1: 16.8 (95% confidence interval (CI) (9.8, 23.8)) CFU vs. Group 3: 17.1 CFU (95% CI (10.1, 24.1)); and $p = 0.616$ for Group 2: 15.3 CFU (95% CI (8.3, 22.3)) vs. Group 3: 17.1 CFU (95% CI (10.1, 24.1)) [5]. Additionally, a study by Sivanandan et al. examined the level of garment contamination by comparing blood agar plates pressed against the OR attire of 20 physicians (at 2-hour intervals during an 8-hour period) who had worn scrubs inside and outside OR attire designated areas [6]. Their results also suggested that the levels of contamination were comparable between the groups that wore OR attire within restrictive OR attire settings and those that wore OR attire outside these settings [6].

Similar results were seen in a study by Kaplan et al., comparing pieces of fabric that were analyzed by traditional cultures in physicians wearing scrubs inside/outside designated zones (including outside the hospital) and also with/without cover garments outside allocated areas [7]. The results were based on a total of 75 participants that each provided fabric samples from 2 sites that were believed to represent areas of likely contamination. In total, 150 samples were collected during the project, 50 from each study arm. The three groups were composed as follows: Group 1: scrubs worn in designated areas and a protective covering was worn when outside these zones and they never left the hospital, Group 2: scrubs worn in designated areas and outside without protective covering and they never left the hospital and Group 3: scrubs worn inside/outside designated areas without protective covering and they were allowed to go outside the hospital. The percentage of agar samples with growth (at 24 and 48 hours) for the various fabric samples taken from each group were as follows: Group 1: 47 and 66%, Group 2: 38 and 56% and Group 3: 56 and 70% of agar samples with growth [7]. The authors determined that wearing cover garments over OR attire did not reduce that rates of contamination and that there were no significant differences ($p = .55$) in groups with attire worn outside the hospital and outside restricted zones [7].

In contrast to the aforementioned studies, a study by Mailhot et al., with a similar design to Kaplan et al., found that there were significant differences in contamination rates of OR attire in comparing nurses with cover garments and those without cover garments when worn in undesignated areas outside OR attire zones [8]. This suggested that the use of cover garments may help decrease the rates of garment contamination when wearing OR attire outside of restrictive areas. However, it remains undecided whether this could reduce the likelihood of patients developing SSIs or PJIs in this setting.

Overall, the above-mentioned studies examined rates of contamination for scrub suits, and not how this impacted the outcomes for patients regarding SSIs or PJIs. Studies directly evaluating if OR attire worn outside the hospital and/or outside the restricted OR area and in relation to the incidence of SSIs/PJIs have yet to be published. Until conclusive evidence is brought forth, OR attire worn outside the operating room remains a potential source for surgical contamination.

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QUESTION 8: Does the methicillin-resistant Staphylococcus aureus/epidermidis (MRSA/MRSE) colonization status of operating room (OR) personnel affect the hospital's rate of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: Unknown. While OR personnel have previously been reported to contribute to environmental contamination, the literature provides insufficient data to establish strong correlations between OR staff colonization with MRSA/MRSE and a potential for increased infections in patients after orthopaedic procedures.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 4%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

MRSA is a common source of nosocomial infections and has been reported as a potential cause of SSIs and PJIs leading to major complications [1,2]. The prevalence of healthcare worker MRSA colonization is estimated to be between 4.6 and 7.9% [3–5]. Some reports have even been published demonstrating higher incidences of up to 76% in special populations [6].

Nasal carriage of *S. aureus* is known to be a major risk factor for SSIs [7,8]. However, the transmission of MRSA from a staff member to a patient is believed to be an uncommon event with only 11 of 191 (5.8%) confirmed outbreaks occurring in this manner in one study [9] Nevertheless, 41% of nosocomial outbreaks (including all pathogens) transmitted by a contaminated staff member occurred in the OR [10].

A total of 10 articles relevant to orthopaedic staff MRSA colonization were included in this review [11–20]. The MRSA colonization rate of orthopaedic staff members in the literature averages at 7.8% (range 0 to 31%, median 4.2%) in 941 screened staff [12–18,20]. Of the studies reviewed, Portigliatti-Barbos et al. (31% penicillin-resistant *S. aureus*), Chang et al. (13.9% MRSA), Faibis et al. (2.3% MRSA) and Schwarzkopf et al. (1.5% MRSA) screened exclusively OR personnel [16–18,20].

Most identified publications did not investigate the infection rates of patients in the context of OR staff colonization with MRSA, thus the available data is limited. De Lucas-Villarrubia et al. [12] evaluated decolonized contaminated staff members and patients and added a broad spectrum antibiotic to their surgical prophylaxis. By introducing these precautionary measures, the SSI rates dropped from 5.9 to 3.0%, the MRSA infection rates from 1.2 to 0.3% and the MRSA PJI rates from 9.7 to 1.0%. Mullen et al. [11] implemented a decolonization protocol of colonized staff and patients and reported a decreased rate of SSIs from 1.76 to 0.33%. Despite reporting the highest staff colonization rates (31% of theater staff), Portigliatti-Barbos et al. [16] showed a reduction of the already low SSI rates of 0.6 to 0% after a five-day decolonization course of intranasal mupirocin ointment for affected orthopaedic surgical team members. Dilogo et al. [13] did not identify any MRSA colonized orthopaedic staff members and concluded that there were no significant associations between MRSA staff colonizations and infections. We did not identify a relevant study investigating (MRSE) within the context of the question.

There is insufficient data available to establish a strong correlation between OR staff MRSA/MRSE colonization and the potential for increased infection rates in patients undergoing orthopaedic procedures. None of the studies re-evaluated the rate of staff colonization after decontamination protocols were initiated. The data sets across the included studies are heterogeneous which impedes pooled statistical analyses. Hence, a direct correlation between reduction in staff colonization and the reduction in MRSA-associated SSIs and PJIs cannot be confirmed, but is currently presumed.

The identified studies support current public health efforts to minimize nosocomial infections in the hospital setting with the focus on best possible patient outcomes. Additional studies are required to screen for MRSA colonization in staff members before and after decolonization, while monitoring the subsequent infection rates in patients.

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1.12. PREVENTION: OPERATING ROOM, ENVIRONMENT

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QUESTION 1: Does the use of laminar airflow (LAF) in the operating room (OR) reduce the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing orthopaedic procedures?

RECOMMENDATION: Recent orthopaedic literature has not demonstrated that the use of LAF reduces SSIs or PJIs in orthopaedic surgery. At this time, is not necessary to perform a clean orthopaedic surgery procedure, including elective joint arthroplasty surgery, in an operating theater equipped with LAF systems.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 81%, Disagree: 14%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The prevention of SSIs and PJIs in orthopaedic procedures requires preparation and optimization of all aspects of patient care, including pre- and postoperative variables, the surgical environment and surgical technique [1–3]. Of the modifiable variables in the surgical environment, air cleanliness has been an area of focus since it was emphasized by Sir John Charnely et al. [4,5]. LAF is described as an entire body of "ultraclean" air within a designated space moving with uniform velocity in a single direction along parallel flow lines. The system moves air with the use of fans through highly-efficient particular air filters (HEPA). The goal of LAF is that air remains flowing smoothly after filtration so that only clean, and filtered air will be directed without interruption or turbulence into contact with the surgical field. This ensures that filtered air should not contact sources of contamination en route to the designated area and that there is no mixing of filtered and unfiltered air [6–8].

Since the introduction of LAF systems, several studies have evaluated its effects on SSIs and PJIs, with most of the orthopaedic literature focusing on total joint arthroplasty (TJA) [9]. Earlier studies suggested that laminar flow ventilation systems were effective at reducing SSIs/PJIs, however, recent studies have not shown a reduction or increase in SSIs/PJIs. Currently, well-designed, high-level studies in this area are lacking. Of the studies initially in favor of LAF, in 1982 Lidwell et al. performed a randomized, multicenter study comparing TJA patients in LAF equipped ORs versus conventionally ventilated ORs. The study showed a markedly reduced incidence of sepsis in the laminar flow group (0.6%) compared to that for the control group (1.5%) in 8,055 patients [10]. However, the authors noted they did not control for the use of antibiotic prophylaxis and exhaust suits, both of which lower the rate of sepsis when utilized [10]. These results were corroborated by Kakwani et al. (2007) who reported 4% infection rates in a non-laminar flow OR compared to 0% ($p = 0.003$) infection rate in LAF ORs in a total of 435 patients undergoing Austin-Moore hemiarthroplasty for hip fractures [11].

On the contrary, a larger body of evidence suggests that LAF is not associated with a reduction in SSIs/PJIs. Marotte et al. retrospectively reviewed 2,384 cementless total hip arthroplasties (THA) performed in LAF vs. non-LAF ORs in 1987. They found no difference in sepsis rates between the two settings and only antibiotic prophylaxis reduced the rate of sepsis [12]. van Griethuysen et al. compared infection rates after switching from a conventional OR to a newer hospital equipped with LAF. They found no differences in infection rates (1.2% before, 1.6% after) between the two sites in 1,687 clean orthopaedic surgeries [13]. Additional large studies utilizing national databases by Singh et al., Breier et al. and Pinder et al. found no reduction in SSIs/infections when surgery was performed in LAF ORs during TJA [14,15] or orthopaedic trauma procedures [16]. Interestingly, three recent studies utilizing large national registries have demonstrated an increase in infections after TJA using LAF while controlling for potential confounding variables [17–19]. Brandt et al. found an increase in THA SSIs performed in operating rooms using LAF (odds ratio (OR): 1.63, 95% confidence interval (CI) 1.06 to 2.52), but no differences in SSIs were seen in total knee arthroplasty (TKA) [17]. Hooper et al. and Tayton et al. both found an increase in PJIs after TJA when performed under LAF (OR: 1.6, 95% CI 1.04-2.47) [18,19]. Gastmeier et al. showed in a systematic review that no individual study showed a significant benefit for LAF in reducing PJI following TKA and only one study showing benefit in the reduction of PJI after THA. However, there were also a total of four studies showing an increase in SSI rates following THA using LAF [22].

One explanation for the wide variability of reported results with LAF could be the many forms of use and no agreed-upon configuration. Laminar flow is a technology that can be employed in many ways, such as vertical flow, horizontal flow, full curtain and no curtain. Systems have different air velocities, array sizes and exhaust locations. In addition, different countries have different national standards (for instance, the UK has a vertical velocity standard of 0.38 m/s, while the US has no enforceable standard at all) [20]. An important weakness of laminar systems, as commonly employed, is that they fail to address the environment outside of the immediate laminar flow zone. Standard vertical laminar systems only treat about a $3m^2$ area, leaving scant room for implant and instrument trays and tables. Unfortunately, laminar systems may actually contribute to the contamination of these areas by blowing bacteria off of personnel and the floor, onto instrumentation and other personnel [21].

Although the routine usage of laminar flow systems in TJA may no longer be recommended, this should not be interpreted to mean that operating room air quality is unimportant. However, hospitals should not feel obligated to expend additional funds for LAF nor should institutions and surgeons suffer liability for surgeries performed without LAF. Adequate intraoperative air treatments, including clean air exchange rates over patient, personnel and instrumentation areas, will remain a critical factor in the prevention of PJIs and merits further investigation. Ideally, air quality standards

for the active operating room, such as those prevalent in pharmacy and clean room settings, should be considered in the future.

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QUESTION 2: Does the use of forced air warming (FAW) during orthopaedic procedures increase the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: There is no evidence to definitively link FAW to an increased risk of SSIs/PJIs. Alternative methods of warming can be effective and may be used.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Maintaining intraoperative normothermia has been shown to reduce perioperative complications including SSI. FAW represents one of the most widely-used methods to prevent hypothermia and maintain intraoperative normothermia. Intraoperative hypothermia has been linked to increased mortalities and morbidities, longer hospital stays, increased requirements for blood transfusion and increased SSI rates. The SSI prevention effects have not been demonstrated in implant surgery, such as total knee arthroplasty (TKA), total hip arthroplasty (THA) and total shoulder arthroplasty (TSA). There has been a concern in the literature about possible contamination of the operating room (OR) air and surgical field with these devices, and subsequent potential increased risk of SSI, especially PJI. Conductive fabric blankets (CFBs) have been suggested as an alternative for intraoperative warming.

Several experimental studies raised a concern for the possibility of intraoperative contamination caused by FAW. McGovern et al. compared FAW and conductive fabric warming (CFW) devices in a simulation of hip and spine surgery with a mannequin used as a patient [1]. They used bubbles generated at the floor and at the mannequin's head to monitor flow of air in the simulated theater and detected significantly increased bubbles close to the surgical field with the use of the FAW devices. They also conducted a clinical review of their infection data between a twenty-month period when FAW devices were used vs. a seven-month period where CFW devices were used, and found a statistically higher rate of deep SSI with the use of the FAW device. The authors noted, however, that their observational study did not account for infection control procedures that changed over the study period or account for several possible differences in patient risk factors, such as obesity and fitness for surgery. Other studies of the same cohorts by these researchers revealed potential impacts unrelated to the change in warming modality, including thromboprophylaxis [2] and methicillin-sensitive *Staphylococcus aureus* screening [3]. Legg et al. measured changes in temperature and air particles at the surgical site in a simulated OR setup with a volunteer patient simulator [4]. They found statistically significant increases in temperature and particle counts with the

use of FAW compared to controls or radiant warming devices. In a follow-up study on a simulated TKA set-up, the authors used a bubble generator with a digital camera to actually visualize airflow disruptions caused by FAW [5].

Similar to the prior study, they showed a significant increase in particle counts at the surgical site and in drape temperatures. They also identified a substantial disruption in the unidirectional airflow when FAW was used. Dasari et al. conducted an experiment where a mannequin was used as a patient and temperature was measured at multiple different heights and locations with the use of FAW, a conductive blanket or a resistive mattress [6]. They found significantly greater temperature increases caused by FAW at patient height locations, whereas, temperatures measured at other heights (floor, head and ceiling) were similar among the three warming devices. They concluded that FAW generates convection current activity in the vicinity of the surgical site which may disrupt laminar air flow. Belani et al. conducted a study with a mannequin draped for a TKA in an orthopaedic room and a bubble generator placed at the head to visualize air currents [7]. Bubbles were counted on sequential photographs at the surgical field and compared between FAW and CFW. The authors found significantly increased bubble counts over the surgical site with FAW and time-lapse photography identified convection currents mobilizing air from the mannequin's head over the drapes and into the surgical field. A recent predictive fluid flow simulation conducted by He et al. on a computer aided design OR showed significant disruption in airflow caused by FAW with a displacement of squames from the floor into the surgical field [8].

Tumia et al. quantified bacterial counts in air samples taken in empty ORs, during normal surgical operations prior to turning the FAW device on, and 15 minutes after turning the warmer on [9]. They had low study numbers to reach statistical significance, but they observed an increase in bacterial counts during regular surgical operations with the warmer off compared to the empty OR and a further increase after turning the warmer on. They concluded that most of the contamination of OR air is secondary to the presence of surgical staff and OR traffic, and that FAW increases contamination to a lesser extent, but this is likely not of clinical significance given that the counts seen were still well below recommendations for ultra-clean air theaters. Albrecht et al. evaluated filter efficiency in the air blower of FAW devices and found that the intake filters used in air blowers were far from optimal efficiency which resulted in colonization of the internal parts of the device [10,11]. They cultured organisms such as *Staphylococcus aureus* and coagulase-negative *Staphylococcus*, which are known to be the major pathogens in total joint arthroplasty. Avidan et al. sampled air coming out of blowers and also found positive cultures in 4 out of 10 devices [12]. However, after connecting the perforated blanket to the air blower and sampling the air coming out underneath the blankets, no organisms grew.

On the other hand, several studies have failed to demonstrate any increased contamination with the use of FAW. Sharp et al. performed a surgical simulation using patients with psoriasis, who are known to have increased shedding of skin [13]. They utilized slit-air sampling and simulated regular OR activity. No bacterial colonies were grown, leading the authors to conclude that FAW did not result in the contamination of the surgical site. Sessler et al. evaluated the effect of FAW on operative room air in laminar airflow conditions using volunteer subjects in an OR with simulated surgical set-up and heated mannequins to simulate OR personnel [14]. A smoke plume was used to visualize airflow and revealed that FAW did not induce any upward draft or any disruption in the normal downward movement of sterile air. A particle counter was used to evaluate changes in particle concentrations near a theoretical incision site. No significant differences were found between having the FAW device off, on ambient air or on warm air. All scenarios had particle counts below stringent criteria established in Europe for the evaluation of adequate function of laminar flow in operating rooms.

Moretti et al. evaluated the effect of FAW on air quality during THA procedures with the use of an air-sampling device with agar plates [15]. No differences in bacterial loads were noted at several positions of the surgical field with or without the use of FAW. Memarzadeh et al. reported computational fluid dynamics and particle tracking studies conducted by the National Institutes of Health to assess whether FAW devices lead to contamination of the surgical site [16]. They found no increased squame deposition from potential contaminant sources due to the FAW device in laminar flow theater situations in their models. Zink et al. evaluated air quality in rooms with volunteers lying down covered by surgical drapes with culture plates placed on their abdomen while FAW was turned on for two hours [17]. Results were compared to a two-hour period where the warmer was turned off. No statistically significant difference was identified between the two situations. Shirozu et al. looked at the effect of FAW on airflow in a simulated operative setting with the use of an ultrasonic anemometer, smoke and laser light [18]. The authors found that downward laminar flow efficiently counteracted the upward airflow caused by FAW blankets and concluded that contamination of the surgical field is not likely in the presence of adequate laminar flow. In a study from the veterinarian literature, two groups of surgical patients were compared (one with use of FAW blankets and one without) [19]. Surgical drapes were swabbed and aerobic cultures were obtained. No difference in positive cultures was noted.

Oguz et al. recently conducted a prospective study where orthopaedic patients were randomized to receive either a FAW blanket or a CFW [20]. They performed a multivariate analysis looking at the effect of multiple factors on the number of bacteria in the OR air and on the field as measured by agar plates positioned at different locations in the room, and nitrocellulose plates placed on the instrument table. These factors included the type of warming device in addition to the presence of laminar airflow, the number of operating room personnel and the operative time. While increased surgical time and absence of laminar flow significantly affected bacterial counts, the type of warming device used did not.

Sikka and Prielipp published a focused review of the literature in the Journal of Bone and Joint Surgery and concluded that there is not enough evidence to support or disprove a link between FAW and PJI [21]. They did list recommendations that need to be followed for proper use of the devices including frequent filter changes, calibration and always using the device with the accompanying blanket. Kellam et al. in a comprehensive review for the Association of Perioperative Registered Nurses (AORN) failed to identify conclusive evidence for an increased risk of SSI with the use of FAW and recommended continued use of these devices [22]. Wood et al. conducted a similar review and concluded that FAW does contaminate ultra-clean air in the operating room, but found no definite link to an increased rate of SSIs [23]. They recommended considering alternative warming systems when contamination of the surgical field is deemed to be critical. In a more recent systematic review that encompassed a total of 1,965 patients and 8 studies, Haeberle et al. concluded that there was an absence of evidence to support an increased rate of SSI with the use of FAW blankets [24].

Sandoval et al. compared FAW vs. CFW in its ability to prevent hypothermia in 120 THA and TKA surgeries [25]. There were 60 patients in each group and they concluded that FAW and CFB were equally as effective at maintaining core temperatures during and after surgery. There were no reported SSIs in either group. This study was a quality improvement project and not powered to show a clinically significant difference in infection rates.

In conclusion, the literature is conflicting and there is still a lack of strong evidence linking FAW to increased risk of SSI. In light of this, while we recognize the theoretical risk posed by FAW, we cannot recommend discontinuing the use of these devices at this time. We do, however, recommend following the manufacturer's instructions and frequently changing the filters, making sure the devices are calibrated and most importantly using the devices only with the appropriate perforated blanket. Other alternative warming methods can be used. We recommend a randomized prospective trial to answer the index question, and a pilot is underway. (ISRCTN 74612906)

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QUESTION 3: Does the operating room (OR) temperature affect the rate of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: The OR temperature may affect core body temperature, which could potentially affect the rates of subsequent SSIs/PJIs. Thus, all efforts should be made to maintain an optimal OR temperature.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 88%, Disagree: 8%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Multiple OR varaibles are known to influence the rates of SSIs/PJIs in patients undergoing orthopaedic procedures. Some of the important issues in the OR are the status of the ventilation system, environmental contamination, including air as well as surface contamination in association with humidity, and temperatures that are known factors sustaining microorganism growth. Clinically used ventilation systems are able to reduce the number of colony forming units (CFUs) near the surgical field. However, systems using vertical laminar airflow and those relying on a newly developed temperature-controlled air flow have been shown to achieve better suppression of environmental contamination that is even more efficacious than classical laminar air flow systems.

Recently-published studies have demonstrated correlations between seasonal temperature changes and SSI rates. SSIs peaked during the warmer season and were lowest in the winter and this in itself could include a multitude of additional environmental factors.

The currently-available literature has not established the ideal OR temperature range, but suggests that temperatures around or below 24°C are preferable. In some countries (e.g., Germany), International Organization for Standardization (ISO) norms describe a

need to select OR temperatures between 18°C and 24°C. We are not aware of any studies about a lower temperature boundary showing adverse effects concerning wound healing, cardiovascular circulation, etc.

Another factor associated with increased temperatures in the OR setting are the increase in transpiration rates among the OR personnel, specifically the surgeon, who may contaminate the surgical field with sweat.

Everett et al. reported that the incidence of SSIs increased when the ventilation system progressively deteriorated. They found with new improved ventilation systems the infections returned to baseline rates. The control of temperature and humidity is important mainly for the comfort of the OR personnel (low-quality study) [1].

Alfonso-Sanchez et al. conducted a longitudinal prospective study to identify the influence of OR environmental factors on subsequent SSIs. Risk factors related to the OR included the level of fungi and bacterial contamination, temperature and humidity, as well as air renewal and differential air pressure. Patient-related variables assessed included age, sex, comorbidities, nutrition level and transfusion. Other factors were antibiotic prophylaxis, electric versus manual shaving, American Society of Anaesthesiologists physical status classification, type of intervention, duration of the intervention and preoperative stay [2]. Superficial SSIs were most often associated with environmental factors, such as environmental contamination by fungi (from two colony-forming units), by bacteria, as well as surface contamination. The environmental factors studied, including the OR temperatures, were found to influence the rates of subsequent SSIs. For example, when there was no contamination in the OR, no SSIs were detected. Significant risk factors in superficial SSIs were environmental contamination by fungi (≥ 6 CFU/m^3, with a relative risk (RR) of 6.2), bacteria, as well as surface contamination by both fungi and bacteria. Also important were humidity, differential pressure and OR temperatures. The OR temperature was associated with superficial SSIs, but not deep SSIs [2].

Fu Shaw et al. noted that the bacterial colony count increased by 9.4 CFU/m^3 with each additional 1°C rise at room temperature ($p = 0.018$) [3]. Another study by Alsved et al. compared two commonly-used ventilation systems (vertical laminar airflow (LAF) and turbulent mixed airflow (TMA)) with a newly-developed ventilation technique and temperature-controlled airflow (TAF), measuring CFU concentrations at three OR locations. They also evaluated comfort on the operating team. The study found that only LAF and TAF resulted in less than 10 CFU/mL at all measurement locations in the room during surgery. Median values of cfu/m^3 close to the wound (250 samples) were 0 for LAF, 1 for TAF and 10 for TMA. Peripherally in the room, the CFU concentrations were lowest for TAF. The CFU concentrations did not scale proportionally with airflow rates. Compared with LAF, the power consumption of TAF was 28% lower and there was significantly less disturbance from noise and draught. [4].

Anthony et al. analyzed 760,283 procedures (total knee arthroplasty (TKA) 424,104, total hip arthroplasty (THA) 336,179) for the influence of seasonal temperatures on SSIs. Their models indicate that SSI risks were highest for patients discharged in June, and lowest for those discharged December. For TKA, the odds of 30-day readmission for SSIs were 30.5% higher at the peak compared to the nadir time (95% confidence interval (CI) 20 to 42). For THA, the seasonal increase in SSIs was 19% (95% CI 9 to 30). (High-quality study) [5].

Another study by Anthony et al. described a highly seasonal variability of SSI, with the highest SSI incidence in August and the lowest in January. During the study period, there were 26.5% more cases in August than in January (95% CI, 23.3 to 29.7). Controlling for demographic and hospital-level characteristics, the odds of a primary SSI readmission increased by roughly 2.1% per 2.8°C (5°F) increase in the average monthly temperature. Specifically, the highest temperature group (> 32.2°C [> 90°F]) was associated with an increase in the odds for an SSI readmission by 28.9% (95% CI, 20.2 to 38.3) compared to lower temperatures (< 4.4°C [< 40°F]) (moderate-quality study) [6].

Mills et al. concluded that the sweating surgeon may most likely contaminate the surgical field as a result of elevated OR temperatures [7].

Based on the available evidence, it appears that OR tempreature is an important enviromental factor that needs to be optimally controlled during surgical procedures. There is an indirect link between the OR temperatures and the potential for subsequent SSIs/PJIs.

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QUESTION 4: Does perioperative normothermia affect the rate of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: Based on data from general surgery and other surgical disciplines, normothermia has been found to be an important factor during the perioperative period, in order to minimize the risks of subsequent infections. Although evidence in orthopaedic surgery is sparse, we recommend that normothermia also be maintained in patients undergoing orthopaedic procedures.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 97%, Disagree: 1%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

Medications used during general anesthesia, such as inhaled and intravenous agents as well as opioids, alter the ability for the body to thermoregulate which may result in hypothermia [1]. Hypothermia can also result from the use of neuraxial anesthesia, except with peripheral nerve blocks [1]. Several animal studies have demonstrated that intraoperative hypothermia may decrease resistance to some pathogens, such as *Escherichia coli* (*E. coli*) and *Staphylococcus aureus* [2,3]. Hypothermia and secondary vasoconstriction may also lead to reduced oxygen delivery to tissues, increasing the risks of infectious complications [4–6]. Several well-designed studies have attributed a substantial decrease in SSI rates in colorectal and non-orthopaedic clean surgeries with normothermia [5,6]. Therefore, current guidelines from the World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) recommend maintaining perioperative normothermia to reduce the risk of SSIs and other complications associated with surgery [7,8]. However, there is a paucity of published literature regarding normothermia in orthopaedic procedures.

In a recent observational study evaluating the role of hypothermia in hip fractures, the incidence of perioperative hypothermia was 17%. After multivariate logistic regression analysis, hypothermia was associated with increased risk of periprosthetic joint infection (PJI) (odds ratio (OR): 3.30, 95% confidence interval (CI) 1.19 to 9.14, p = .022) [9]. In contrast, from another observational study evaluating total hip and knee arthroplasties, no statistically significant associations were found between hypothermia and PJIs or SSIs in univariate analysis [10]. Observational studies [10–13] have associated hypothermia with increased blood loss and transfusion rates, which may subsequently lead to increased risks for PJIs or SSIs. However, there are no randomized controlled trials (RCTs) that support nor discourage normothermia in total joint arthroplasty (TJA) or other orthopaedic procedures in relation to SSIs or PJIs.

There are several RCTs that have been performed outside of orthopaedics, which support the use of warming devices in the operating room and during the surgical procedure for the purposes of reducing SSIs [5,6]. Kurz et al. evaluated the importance of maintaining perioperative normothermia with additional warming in major colorectal surgery patients [5]. The mean final intraoperative core temperature was higher in those with additional warming compared with those without (36.6 vs. 34.7 °C, p < 0.001). Patients assigned to additional warming demonstrated a significant decrease in SSI rates by receiving forced-air warming blankets combined with fluid warming (6 vs. 19%, p = 0.009). In another RCT, Melling et al. evaluated patients undergoing non-orthopaedic clean surgeries and identified a substantial role of pre-warming in preventing SSI [6]. They showed that warming the patient for at least 30 minutes before surgery led to a reduction in infection rate from 14 to 5% (p = 0.001) [6].

The safest and most effective mode of maintaining intraoperative normothermia remains unknown. Some recent studies have raised potential issues with the use of forced-air warming systems that may disrupt the laminar airflow (LAF) in operating rooms and increase risks for SSIs [14–16]. But, from a recent experimental study, disruption of airflow produced by forced-air warming was well-counteracted by downward LAF from the ceiling [17]. There are no studies which provide high-level evidence that warming systems may increase infection rates.

In summary, achieving normothermia by using warming devices in the operating room and during the surgical procedure seems to play an important role in decreasing the risks of subsequent infections. However, this evidence mainly derives from non-orthopaedic literature. Further research is needed to establish correlation between patient's temperature and SSIs in the field of orthopaedic surgery, including TJAs.

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QUESTION 5: Is there a relationship between levels of airborne microorganisms in the operating room (OR) and the risk of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Yes. High-quality evidence indicates that there is a proportional relationship between intraoperative levels of airborne microorganisms (colony-forming units or CFUs) and the incidence of PJIs.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive search was performed utilizing PubMed and Google Scholar with the keywords: operating room air, airborne microorganisms, implant, infection, surgical site infection, Charnley and Lidwell. A total of 248 potentially-relevant articles were identified and reviewed. After screening for relevance to the topic of airborne microorganisms and PJI, 34 articles were selected for analysis. Of these, to the best of our knowledge, only five studies that adequately compare airborne CFU levels during actual surgical operations and the incidence of SSI have been published [1–5].

Four of these five level of evidence I studies demonstrate statistically significant correlations between levels of airborne CFUs (measured either by active air sampling at or near the incision site or by wound washout) and the incidences of PJIs [1–4]. The fifth study compared airborne CFUs and postoperative infections in three ORs with conventional ventilation to the data obtained in one-zoned, exponential laminar airflow (LAF) OR, and found no difference in the incidence of PJIs [5]. However, the study also found no difference in airborne CFU present in the LAF OR and the conventionally-ventilated rooms, which is consistent with the hypothesis that PJIs are correlated to the level of airborne CFUs in ORs.

One study retrospectively performed a multivariable regression analysis of data from a large prospective UK study, and concluded that prophylactic antibiotics were effective at reducing the incidences of PJIs. However, the group also found that this variable was independent of the presence of ultra-clean air, suggesting that the two modalities are multiplicative [6]. The conclusions of this study must be weighed against the facts that antibiotic prophylaxis was not controlled during the main study and perioperative antibiotic use varied widely.

The literature review demonstrated common characteristics that limited their clinical relevance. The use of the term "laminar flow" to describe air patterns in the OR and equating this term with "ultra-clean" air is potentially misleading. There are a host of variables in a busy OR that can disrupt laminar flow, and there are many different manufacturers and types of "laminar flow" configurations. Examples include, rising thermal plumes caused by heat from operating room lights, opening of doors which causes positively-pressurized air to escape into hallways thereby shifting air currents and turbulence created when air passes overhead surgery lights and the torsos of the surgical staff [7–9]. It is therefore, important to assess the ability of ORs labelled as "laminar flow" to actually provide a reduction of airborne CFUs, compared to conventionally-ventilated operating rooms. For example, one study of 3,175 hip and knee arthroplasties using a "horizontal unidirectional filtered air-flow system," reported mixed infection reduction results, but no airborne CFU data was obtained, perhaps because it was assumed that the "laminar flow" rooms provided clean air [10]. Other studies suffered the same issue of not reporting airborne CFUs together with infection data [11–12].

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QUESTION 6: What method(s) are available to verify the microbiological cleanliness of the operating room (OR)?

RECOMMENDATION: Multiple options are available to verify the microbiological cleanliness of the OR, including visual inspection, swab and culture, contact culture plates, as well as Adenosine Triphosphate (ATP) bioluminescence.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 1%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

We are continuously striving to minimize periprosthetic joint infections (PJIs) due to their association with higher morbidity and mortality [1–3].

The original standard for determining cleanliness within hospitals was visual inspection until multiple studies proved it inferior to newer, more quantitative methods [4–9]. The major drawbacks to visual inspection include, the subjectivity of the analysis, that it cannot provide any information as to what microbes are on the surfaces, and the qualitative nature, which has consistently been shown to be less sensitive than other evaluation methods [4–9].

In order to standardize monitoring of microbial cleanliness in the OR, cultures via swabs or contact plates that determine the colony forming units (CFUs) were introduced as an objective measure, with particular attention paid to high-touch surfaces [6,10–16]. Cultures utilizing aerobic colony counts (ACC), with or without bacterial specific growth parameters, provide a general overview of the microbial burden in the OR [10,11,17]. It is generally accepted that cultures < 2.5 CFU per cm^2 are considered clean and anything greater, considered contaminated [5,6,10,11,15,17,18]. The limitations of this method include, the length of time it takes to achieve results by culture (generally at least 24 hours for pure CFU counts and 48 hours for bacterial speciation), limitations in the ability to culture certain bacteria and that it cannot account for other bioburden contaminating surfaces such as body fluids, blood and saliva.

ATP bioluminescence is a technology that has long been used in the food industry to monitor cleanliness and has recently been introduced in the OR [19–21]. The amount of ATP produced by live cells is measured in relative light units (RLUs) with standards set by the manufacturer. There is currently no agreed-upon standard RLU value to be used as a benchmark for signaling clean versus contaminated. Most of the studies to date use a value of 250 to 500 RLUs as the benchmark for cleanliness [6,7,13,17,22–24]. While conflicting evidence exists attempting to correlate ATP with CFU counts [6,7,9,13,16,17,22–24], more stringent comparative studies with outcomes are needed to determine the benchmark RLU values that decrease the risk of PJIs. This method is rapid and allows for assessments of the overall bioburden in the OR, including body fluids [13–15,22–24]. The limitations of ATP are the cost and inability to determine what specific pathogen is contaminating the OR when high readings occur [9].

With the limited literature available, we extrapolate that use of ATP bioluminescence provides the greatest utility as a fast feedback method to monitor the cleanliness of the OR on a regular basis. We recommend using a value of 250 RLUs as the benchmark value for contamination. Furthermore, surfaces that consistently provide high readings of the ATP meter can be swabbed and cultured for CFU counts (> 2.5 CFU/cm^2 considered contaminated) and microbiological speciation.

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QUESTION 7: Does the use of ultraviolet (UV) light decontamination in the operating room (OR) reduce the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing orthopaedic procedures?

RECOMMENDATION: Yes, the use of UV lights during surgery are effective against airborne bacteria. However, due to the potential risks to the OR personnel, it is recommended that UV light only be used at unoccupied times for terminal cleaning of the room.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 91%, Disagree: 4%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The source of a large portion of the microorganisms responsible for PJIs are the airborne microorganisms in the OR [1]. The room traffic, door status and number of people in the room are the basic indicators of the quantity of airborne colony-forming units (CFUs) [2]. To reduce the number of airborne CFUs in the OR during surgery, techniques are applied such as surgical gowning with air outlets, the use of laminar airflow, a reduction in room traffic and the application of UV lights [2,4–7].

The efficacy of techniques designed to remove airborne bacteria from the OR is supported by current randomized controlled trials (RCTs) studies [1]. In the OR, a concentration of 10 m^{-3} or less airborne bacteria is defined as ultraclean air [2]. UV light at specific wavelengths breaks the molecular bonds in the DNA, thereby eliminating microorganisms that may cause subsequent infections. Since the first application, a relationship has been shown between different UV wavelengths and a decrease in infection rates with a reduction in CFUs or the obtaining of ultraclean air [3–5]. The first data related to the use of UV light during surgical procedures was from Duke University. With the use of UV light in all types of surgery in 1936, the infection rates and infection-related mortality rates decreased from 11.3 and 1.3% pre-1936 to 0.24 and 0% in 1960, respectively [6]. In a 1980 study, the rate of PJI following hip arthroplasty was reduced from 3.1 to 0.53% with the use of UV light [7].

In a randomized study of 30 hip arthroplasties performed by Carlsson in 1986, the use of UV lights in the OR were shown to significantly reduce the number of CFUs, both in the wound area and in the periphery of the room, as determined by volumetric air samples [8]. Another pioneering study in this field was conducted by the same team in 1989 [9]. The combined method of occlusive staff clothing and UV radiation was used and the air samples from 20 cases of hip arthroplasty were all reported as < 10CFU/m^3, which is the limit for "ultraclean air" (median 2.6, range 1.1 to 7.1).

In 1991, Berg et al. reported that UV lights were more effective than the ultraclean air enclosure method and applications of UV combined with occlusive clothing reduced infection [10]. Taylor et al. conducted a similar cohort study in 1995, in which different doses of UV lights were compared with laminar flow and conventional ventilation. Again, results favorable to UV lights were obtained [5]. Berg-Perier et al. compared the UV light method with the Charnley-Howorth ultraclean air enclosure in an economic, comfort and safety analysis and presented data that UV light was superior in respect to cost, comfort and safety when sufficient protection was provided [11].

One of the most important studies conducted was by Ritter et al. In their retrospective cohort study published in 2005, the infection rates of 5,980 joint arthroplasties were examined [12]. It was shown that the infection rate of 1.77% with the laminar flow before the application of UV light had decreased to 0.57% after the use of UV light without laminar flow ($p < 0.0001$).

Although several studies support the efficacy of the use of UV lights against airborne bacteria during orthopaedic surgical procedures, because of the potential side-effects on OR staff, this application has been restricted by the guidelines, and there are even recommendations that it should not be used [13,14].

There is no current data available related to the possible reduction of the use of UV lights during surgery in accordance with the guidelines and reported side-effects. New designs have been developed which could increase the safety of OR staff and provide maximum air disinfection effectiveness. However, there are no publications of the clinical efficacy of these new designs in respect to both of these aspects [15]. Possibly the most important area that could benefit from the germicidal effectiveness of UV light decontamination is terminal room cleaning of the OR or hospital rooms at unoccupied times.

The Tru-D (Tru-D Smart UVC, Memphis, Tennessee, USA) room disinfection device is a mobile, automated room disinfection device that uses UV-C irradiation to kill microorganisms. In an Mahida et al., the efficacy of the Tru-D device was evaluated in the terminal cleaning of patient rooms and the OR. It was reported that the mean log^{10} reductions for artificially seeded methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *enterococci* (VRE) were between three and four when used at 22,000 mWs/cm^2 reflected dose [16]. Similarly, through evaluation of logarithmic reductions, several studies have shown the effectiveness of UV devices in the inactivation of microbes seeded on various test surfaces placed in occupied hospital rooms [17–22]. Several clinical trials have also measured the effectiveness of UV devices in terminal room cleaning and have

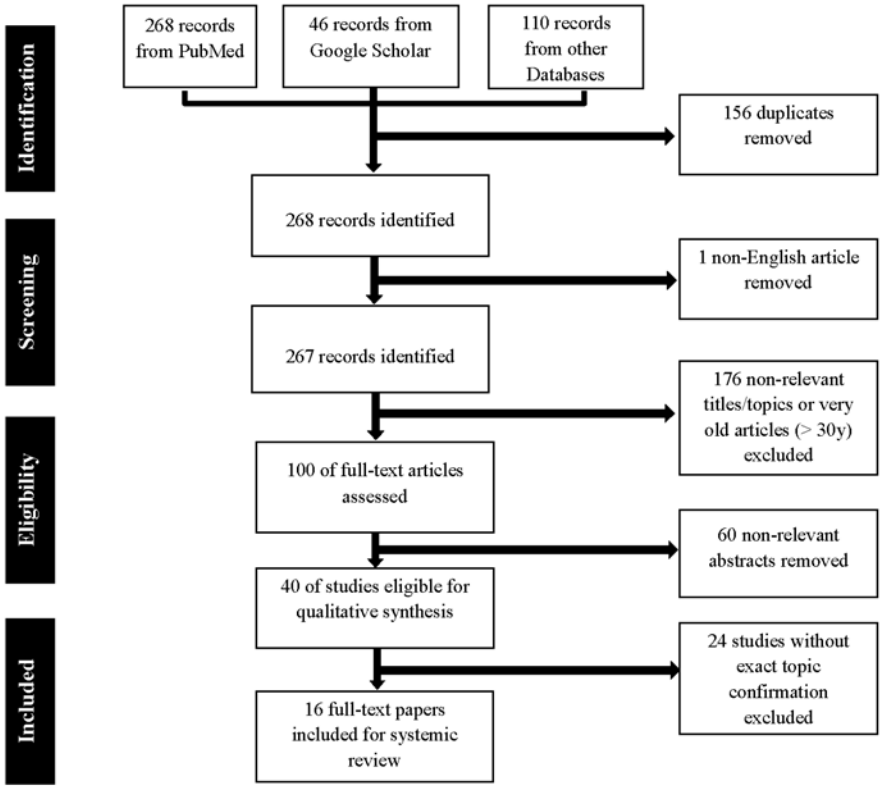

FIGURE 1. PRISMA Flowchart showing the identification of relevant studies during the review process.

shown statistically significant reductions in the rates of healthcare-associated infections (HAIs) [23–26]. The only randomized, controlled study in this area, is a multi-center study by Anderson et al. that included nine hospitals. The terminal room cleaning method using the Tru-D device was utilized in two of four control groups formed of different combinations. The use of advanced room cleaning strategies, such as a UV device, was shown to reduce HAIs in every 10,000 cases from 51.3 to 33.9 ($p = 0.0369$) [27].

Furthermore, Fornwalt et al. reported on the efficacy of pulsed xenon ultraviolet lights on SSIs in patients undergoing total joint procedures in 2016 [28]. They found a significant reduction to zero infections after 12 months of surgery by renovating their orthopaedic surgery wing and by implementing new stringent procedures and pulsed xenon (PX)-UV decontamination before surgery.

Based on the overall evidence compiled (Fig. 1), despite the efficacy of UV light during surgery against airborne bacteria, its use is not justified due to the risks that could be created for operating room staff. However, evidence exists supporting the use of UV lights for the terminal cleaning of rooms at unoccupied times.

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QUESTION 8: Are light handles a source of contamination during orthopaedic procedures?

RECOMMENDATION: Yes. Light handles are a possible source of contamination during orthopaedic procedures.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 96%, Disagree: 3%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Periprosthetic joint infections (PJIs) are a morbid complication following total joint arthroplasty, with increased mortality at one year [1]. Since the recurrence rate after treatment of PJI at five-year follow-up can reach up to 60% [2], prevention in the perioperative phase is essential. Despite several behavioral and technological developments, bacteria cannot be fully eliminated from an operating room (OR) [3]. Therefore it is very important to examine and identify all possible surfaces in the OR, such as light handles, that could provide an optimal medium for bacterial growth.

A paper presented at the American Academy of Surgeons in 2017 showed that placement of surgical light handles produced moderate particle contamination of the sterile field. A study by Davis et al. concluded that 14.5% of light handles were contaminated during primary hip and knee arthroplasties. Follow-up of a minimum of two years revealed one deep infection in the cohort, however, the organism was not identified as a contaminant [4]. Knobben et al. studied the transfer of *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Cutibacterium acnes* (formerly *Propionibacterium acnes*) from one OR material (gloves, orthopaedic drills, theater gowns and light handles) to another. Transfer was demonstrated with all bacterial strains and with every material ranging from 17 to 71% [5]. In contrast, a study by Hussein et al. examined OR contamination by culturing bacterial swabs taken from light handles before and after 15 total hip and knee arthroplasties. They found no aerobic bacterial contamination after 48 hours of culture on either the surgical gloves or the light handles [6].

A randomized clinical trial by Schweitzer et al. screened 36 light handles in hip arthroplasty for bacterial contamination using two different culture methods, including one with high sensitivity. Positive cultures were found in 50% of the light handles [7]. In a more recent study by Richard et al., a novel method, utilizing adenosine triphosphate bioluminescence technology, was applied to detect the degree of contamination within the sterile OR environment. They concluded that several surfaces, including light handles, had significant bioburdens [8]. This study demonstrated that bioburden can lead to contaminated OR surfaces, and therefore, increase the risks of postoperative orthopaedic infections [8]. The International Consensus Meeting on Periprosthetic Joint Infection and a meta-analysis by Ratto et al. concluded that light handles can be a potential source of contamination and surgeons must minimize their contact with them as much as possible [9,10].

Despite the fact that one study did not find any contamination, several observational studies have identified positive bacterial cultures on light handles utilizing different techniques, with varying sensitivity. We infer that light handles are a possible source of contamination during orthopaedic procedures. However, there is no supporting evidence or prognostic studies that have linked the contamination on the light handles to patients developing subsequent PJIs with the same source contaminant. We do advise surgeons, as a precautionary measure, to minimize contact with the light handles by utilizing their staff to move the lights during the procedure. If contact with the lights is necessary, we also recommend changing gloves in order to limit contamination to the operative field.

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QUESTION 9: Is there a role for banning all handheld devices/mobile phones in the operating room (OR)?

RECOMMENDATION: Given a lack of evidence correlating increased infection rates/adverse outcomes with the use of handheld devices in the OR, a recommendation to ban these devices in the OR cannot be made at this time. However, regular cleansing of cell phones is an easy and effective practice and should be performed routinely.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 87%, Disagree: 8%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Non-medical electronic equipment, such as cell phones, personal digital assistants and wireless media tablets (e.g., mobile handheld devices) have become increasingly integrated into the practice of healthcare workers [1,2]. Previous studies have shown that 33 to 88% of surveyed healthcare workers admit to using cell phones in ORs [1,3,4]. Sergeeva et al. found that mobile devices allow easy information access, e-learning and work-related communication [5]. The potential for these devices to be a source of distraction from the work environment [5], as well as be a nidus for contamination, warrant further examination into whether or not handheld devices/mobile phones should be permitted from the OR.

Phone calls were found to be one of the most frequent distractions in the OR [6–8]. Avidan et al. found that cell phone calls caused short-lived disturbances to the operating surgeons [9]. Murji et al. identified that pager distractions hindered the ability to successfully complete the surgical task in the allotted time and the majority of residents made at least one unsafe clinical decision during the distracted phase [10]. In addition, it has been suggested that ringing telephones are among the major sources of unnecessary noises in the OR [11]. In the study performed in a tertiary care hospital in China, the noise level in the ORs ranged between 59.2 and 72.3 dB, with 100% of the measurements exceeding the recommended hospital noise standards [12].

Excessive noise may have negative effects on patient care and safety. Kurmann et al. showed that ORs with a high noise level also experienced higher surgical site infection (SSI) rates [13]. Simulation-based experiments have identified that noise during surgery can increase feelings of stress, as measured by perceived task load and fatigue levels, [14] cause a decrease in auditory processing function leading to possible miscommunication [15,16] and may impair the ability to accurately monitor pulse oximeter auditory displays [17]. Staff member education on noise reduction strategies (including avoiding conversations on the telephone) have helped to substantially reduce the noise level during the OR procedures [11].

The risk of handheld devices contributing to possible bacterial cross-contamination in the OR must also be discussed. Numerous studies have documented the bacterial contamination of the mobile phones of the healthcare workers [18]. The bacteria species most frequently isolated from the cell-phones (such as coagulase-negative staphylococci and *Staphylococcus aureus*) are known to commonly cause periprosthetic joint infections [1,3,4,18,19]. Genetically identical isolates have been detected from mobile phones and palms and fingers or nares of their users [19,20]. However, it is unknown whether there is a correlation of handheld device contamination with SSI rates, and/or microorganisms causing these infections. In the studies performed in ORs, the mobile phone contamination rate with possible clinical pathogens varied from 0 to 83% [1,3,4,19]. The reason for the large variation of contamination rate may be due to the sampling from different types of handheld devices, different sampling methods, different sampling place and whether coagulase-negative staphylococci have been counted as pathogenic [4,19].

Touchscreen mobile devices have been associated with lower rates of bacterial contamination when compared with traditional keypad alternatives [21]. Shakir et al. reported lower bacterial loads on cell phones with a screen protector [3]. Nevertheless, these devices also need to be regularly decontaminated with approved disinfectant that will not cause damage to the phone [2]. Standardized decontamination protocol significantly reduced bacterial load on the phone [3,4]. In the study by Shakir et al., the contamination rates increased from 8% after disinfection to 75% one week after decontamination, arguing for regular cleaning (several times a week) [3]. The risks of the handheld devices contributing to bacterial cross contamination can be reduced by appropriate hand hygiene. Mark et al. speculated that the higher hand hygiene compliance rates (97%) in their unit could be the reason for lower mobile phone contamination rate [1]. Staff education is essential as the studies indicate that most of the health care workers do not regularly clean their devices or perform hand hygiene before or after use [1–4].

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1.13. PREVENTION: OPERATING ROOM, SURGICAL ATTIRE

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QUESTION 1: Does changing surgical gowns during prolonged operations reduce the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs)? If so, how frequently should gowns be changed during the procedure?

RECOMMENDATION: We cannot recommend for or against gown changes at specific time intervals, as there are no studies evaluating the temporal associations with gown contamination. We do, however, recommend that surgical gowns be changed if saturation or perforation of the gown occurs during surgery.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 97%, Disagree: 2%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

The sterilized surgical gown was first donned by Gustav Neuber in 1883, and soon after their introduction to the operating room (OR), a decrease in surgical infections was reported. Prior to this paradigm shift in surgical attire, surgeons wore a favorite coat, perhaps, which was often soiled from previous operations [1]. Due to the wide variation of surgical gowns available, there is no consensus for which gown design is most efficacious for the prevention of SSIs. Presently, data supports the use of impermeable gowns and further research into disposable versus reusable gowns with regard to the prevention of deep SSIs is required [2–7]. There is no available literature to suggest that changing an otherwise well-functioning gown intraoperatively is of any benefit with regard to the prevention of SSIs or PJIs.

Based on several studies that suggest an increase in contaminants on the OR back table as well as on operative gloves, it stands to reason that prolonged time in the OR also increases contaminants on surgical gowns. According to Dalstrom et al., there was a time-dependent contamination of open sterile trays on the back table with 4% of trays contaminated at 30 minutes, 15% contaminated at one hour, 22% at 2 hours, and 30% at 4 hours [8]. Al-Maiyah et al. performed a randomized control trial (RCT) comparing the frequency of glove changes in two groups of orthopaedic surgeons performing total hip arthroplasties (THAs). One group of surgeons changed gloves every 20 minutes during THA, the other group of surgeons only changed gloves at the time of component implantation. The study demonstrated significant reductions in glove perforations and contaminations in the 20-minute group [9]. Kaya et al. performed a study with a similar scope and determined that glove perforation occurred approximately every 90 minutes during surgery. The group advocated glove changes after this time interval [10]. There is no published data, however, to suggest specifically that changing gowns during prolonged surgical cases ultimately reduces the rate of contamination or, furthermore, deep surgical infections in arthroplasty.

In a study assessing the sterility of various areas of the surgical gown during spine procedures, Bible et al. found that after an average

duration of 134 minutes the contamination rate of impermeable disposable gowns ranged from 6 to 48% depending on location. The highest levels of contamination were at the shoulders (48%) and the bottom of the gown (26%) and the least contamination at the level of the chest (6%) [11]. Based on the results of this study, there is, at a minimum, some documented evidence that gown contamination occurs at 134 minutes to varying degrees on the surface of surgical gowns. Flaherty et al. also demonstrated that the permeability of gowns increases after contact with blood after one hour, potentially increasing contamination [12]. Further investigation is required, however, to specifically answer how often surgical gowns should be changed during prolonged procedures, if at all.

In the absence of definitive data to support changing gowns intraoperatively, this practice should be left to the discretion of the surgeon. However, it is worth keeping in mind that several studies have linked increased surgical time directly with an increase in PJIs and thus, all efforts toward efficient completion of the operation should be made [13,14]. In a study of 69,663 primary TKA patients, 1,400 of which went on to develop a deep postoperative infection, Kurtz et al. reported a hazard ratio of 1.59 for surgical times greater than 210 minutes, as compared to cases performed in less than 120 minutes [15]. Several European registry-based studies and the American College of Surgeons National Surgical Quality Improvement Program (ACS-NSQIP) corroborate these findings and identify surgical times as an independent risk factor for infections [16–18]. In a recent American registry-based study of 56,216 TKAs, a subgroup analysis found a 9% increase in the risk of deep surgical site infections per every additional 15 minutes of operative time (95% confidence interval (CI), 4 to 13%) [19]. In light of this evidence, reasonable efforts should be made to perform surgery in an efficient manner, mitigating time consuming steps and procedures that do not have an evidence-based effect on outcomes.

In conclusion, there is no direct evidence in the literature to support changing gowns during prolonged operations in order to prevent SSIs or PJIs. There is data, however, to suggest that longer operative times increase contamination on surfaces, including the surgeon, as well as evidence that demonstrates an increase in SSIs with increased operative times. With the current literature, as presented, we cannot recommend for or against the proposed intervention, but do highlight that operations should be performed in as efficient a manner as safety and technique allow.

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QUESTION 2: Does the type of surgical gown (disposable or reusable) used by the operating room (OR) personnel affect the rate of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing orthopaedic procedures?

RECOMMENDATIONS: Unknown. The available low-level evidence suggests that disposable gowns may have a higher ability to prevent bacterial dispersion in the OR. Evidence to demonstrate that gown type influences SSI/PJI outcomes is lacking.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 94%, Disagree: 3%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [1] aimed to identify whether the type of surgical gown, disposable or reusable, could affect the rate of postoperative wound infections in orthopaedic surgeries (Fig. 1). A search of the Embase, Scopus, Cochrane, PubMed and Google Scholar search

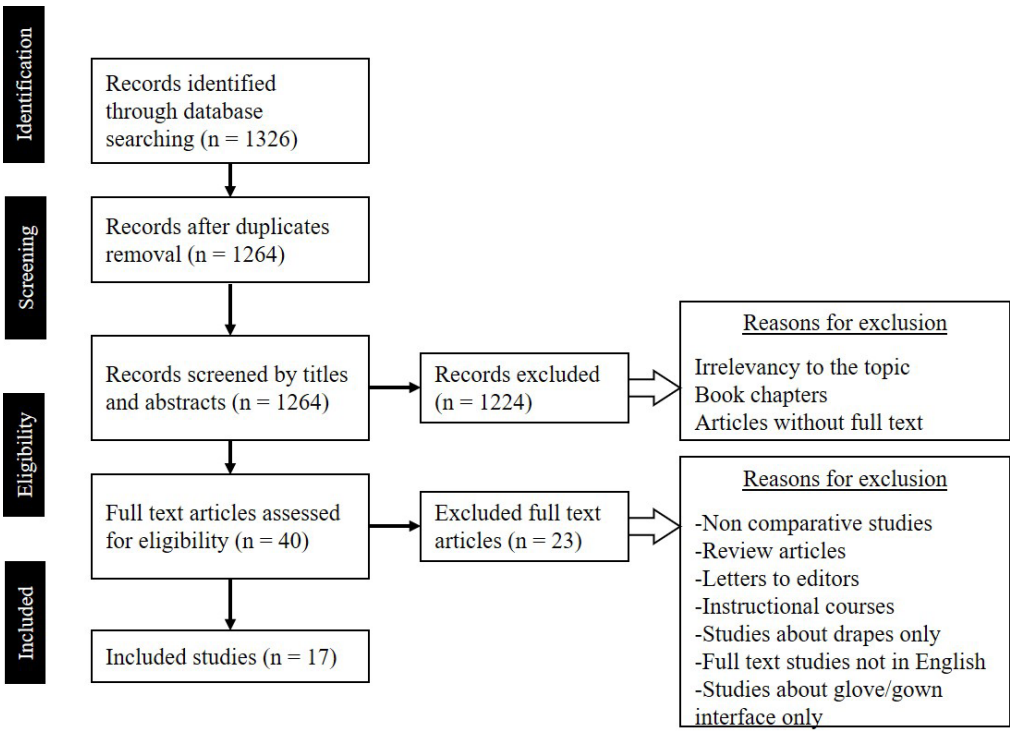

FIGURE 1. Study selection for the systematic review.

engines was conducted using various combinations of the keywords: "Disposable gown," "Reusable gown," "Surgical attire," "surgical gown," "orthopaedic," "arthroplasty" and "infection." No limit was set regarding the year of publication.

The initial search provided a total of 1,264 records after adjustment for duplicates. Of these, 1,224 studies were excluded by title/abstract for clearly not meeting inclusion criteria. The full text of the remaining 40 citations was examined in detail and a further 23 were excluded as outlined in (Fig. 1). A total of 17 full text studies written in English were included in the quantitative synthesis of the review (Fig. 1).

We divided the 17 reports into 2 groups, the first including studies reporting the amount of bacterial penetration and OR contamination in relation to the surgical gown material and the second including the studies reporting about the type of gown and incidence of postoperative SSI.

Of the 17 studies included, 10 reported on gown contamination [2–12], which was expressed as gown bacterial count or penetration, air contamination and wound contamination, 6 reported on deep infection rates [13–18] and 1 reported on both outcomes [19]. Data were based on orthopaedic procedures in seven studies, and on non-orthopaedic procedures in seven studies, non specified procedures in two studies, and one study was in vitro (Tables 1 and 2). Quality assessments of the 16 studies are based on the American Academy of Orthopaedic Surgeons' (AAOS) criteria for observational and randomized trials and all of the Level of Evidences ranged between moderate to low/conflicting evidence [20].

Despite decades of research, there remains a lack of consensus regarding certain aspects of optimal aseptic technique, including selection of surgical gown type [21]. The presence of bacteria on surgical gloves or gowns, along with airborne bacteria or persistence of bacteria on the skin after skin prepation and subsequent contamination of surgical incision, are considered the principal causes of infection in the operative setting [22].

Surgical gowns, as defined by the Food and Drug Administration (FDA) in 1993, are "surgical apparel worn by operating room personnel during surgical procedures to protect both the surgical patient and the operating room personnel from transfer of microorganisms, body fluids, and particulate material." These gowns can be further sub-divided into standard performance or high performance, based upon their ability to allow simulated bacterial/contaminated talc strikethrough in laboratory studies [2]. The testing conditions are done on dry and wet samples and a ratio known as the barrier index is determined for each material. A barrier index of 2.8 is required for standard surgical gowns and a barrier index of 6 is deemed impenetrable, which is required for high-performance surgical gowns [2].

Although there is some conflicting evidence, there seems to be a consensus in the research that impervious surgical gowns are an essential part of reducing SSIs/PJIs in patients undergoing any surgical procedure [21,23–26]. Disposable paper gowns demonstrated less bacterial transmission in the laboratory and lower rates of contamination in the OR [21]. The research indicates that reusable gowns have a high strike through rate when compared with disposable gowns especially at the cuffs, forearms and thighs [21,25]. Similarly, in relation to drapes, it has been shown that reusable woven drapes showed a higher permeability to bacteria when compared to their non-woven disposable counterpart [27].

Despite a World Health Organization (WHO) report in 2016 which stated, "No recommendation is available on the use of disposable or reusable drapes and gowns," [3] there is some laboratory research available which has shown disposable gowns have a lower strike through rate and hence a lower chance of bacterial contamination [21].

Surgical gowns may function to prevent SSIs, either by preventing skin organisms from direct contact from the surgery team's skin and clothing to the surgical site, field or instruments and/or preventing bacteria from reaching the air, which may later settle into the OR areas and surgical wounds [28]. In this systematic review, we tried to present the available data about the relationship between the types of surgical gown, being disposable or reusable, and the risk of surgical wound infections.

All of these studies showed that disposable gowns that were made of different materials (Table 1) showed better resistance to gown material contamination, OR air bacterial load and surgical wound contamination. From these results, low evidence could be deduced that disposable gowns, made of polyester or polypropylene material, as well as the total body exhaust suits, worked much better as barriers for bacterial penetration that might lead to OR air and/or wound contamination. However, there are many other variables that could potentially affect dispersal of bacteria that were not controlled for in most of these studies. For instance the number of people in the OR seems to be one of the most important factors in bacterial air contamination and most studies did not account for this. Another study reported that the barrier provided by reusable gowns diminishes with laundering and is dependent on controlling all variables during reprocessing of the garment [29]. These unresolved issues can potentially reduce the evidence obtained from these studies.

Although the results of the first group of studies may possibly be interpreted by a reviewer as the non-disposable gowns can potentially reduce surgical wound infection by reducing bacterial load in the surgical gown, OR air or surgical wound, yet the studies from group 2 (Table 2) showed variable conflicting results. All the non-randomized studies concluded either a significant [13,14,16] or slight reduction [19] in the deep SSI rates with disposable gowns. Being non-randomized with many uncovered research aspects, the evidence they present ranges from low to very low. On the other hand, the three randomized studies (two randomized, one semi-randomized control trial (RCT) [15,17,18] have shown, with moderate to low evidence, that both types of gowns have comparable SSI rates. Again, there are many factors that were not controlled in these studies in Table 2 that could potentially affect the incidence of SSIs.

TABLE 1. Studies reporting bacterial penetration in relation to the gown type

Study/Year	Type of Surgery	Primary Outcome	Type of Gown		Result/Conclusion
			Single Use	Reusable	
Alford 1973 [4]	Not specified	Gown contamination (index for resistance to bacterial penetration through the gown)	Paper, Plastic	Cotton cloth	Plastic, hooded gown had less microbial contamination than either the cloth or paper gowns by 71.8 and 57.3% ($p < 0.0005$)
Whyte 1976 [5]	Total hip arthroplasty	Air contamination	Disposable non-woven, total body exhaust system (TBES)	Reusable cotton gown	30% reduction in bacterial counts when a disposable non-woven and 10-fold reduction in bacterial particles when a total body exhaust system was used. Authors recommended disposable gowns.
Blomgren 1983 [19]	Elective total hip arthroplasty	Air and wound contamination	Disposable with body exhaust system (TBES)	Conventional reusable cloth	OR air bacterial counts and deep wound infection rates were found to be significantly higher in the conventionally clothed group.
Whyte 1990 [6]	Total hip arthroplasty (Mainly)	Air contamination	Disposable polyester, total body exhaust system (TBES)	Conventional cotton gown	Disposable gowns and TBES showed comparable significant reduction in airborne bacterial dispersion as measured by bacterial air samplers, as compared to reusable gowns.
Sanzén 1990 [2]	Total hip arthroplasty	Air contamination	Disposable non-woven or total body exhaust gowns.	Cotton Cloth	With the disposable gowns and the exhaust suits, the median air contamination with CFUs has been significantly reduced. The authors conclude that both specially-designed scrub suits and exhaust gowns can further reduce an already low-level of bacterial air contamination in a down-flow, clean air enclosure.

TABLE 1. Studies reporting bacterial penetration in relation to the gown type (*Cont.*)

Study/Year	Type of Surgery	Primary Outcome	Type of Gown		Result/Conclusion
			Single Use	Reusable	
Scheibel 1991 [3]	Total hip arthroplasty	Air and wound contamination	Disposable polypropylene gowns	Conventional cotton clothing	Polypropylene coveralls reduced the bacterial contamination of the air of a conventionally ventilated operating room by 62%. The contamination of surgical wounds during joint replacement was also reduced, but not to a significant degree.
Verkalla 1998 [9]	Elective coronary artery bypass surgery	Air contamination	Polypropylene disposable air suits (exhaust suits)	Cotton cloth	With the disposable polypropylene air suits (along with other protective measures),the bacterial air counts decreased from 25 CFU/m3 to 7 CFU/m3, and postoperative surgical wound contamination was significantly reduced.
Tammellin 2001 [10]	Cardiothoracic surgery	Air and wound contamination	Tightly woven disposable cotton/ polyester suits	Conventional reusable suits	Use of tightly-woven special scrub suits reduces the dispersal of total counts of bacteria and of *S aureus* from staff in the operating room, thus possibly reducing the risk of airborne contamination of surgical wounds.
Lankester 2002 [11]	Total hip arthroplasty, total knee arthroplasty	Gown contamination (index for resistance to bacterial penetration through the gown)	Fabric 450'	Theta Barrier fabric woven polyester	Disposable gowns showed statistically significant reduction in bacterial penetration through the surgeon's axilla ($p = .0.02$), the groin ($p = .0.02$) and the peri-anal region ($p < 0.01$), compared to the reusable gowns. Authors recommended against the use of these tested reusable gowns in orthopaedic implant surgery.
Ward 2014 [21]	Clean orthopaedic procedures	Gown contamination (index for resistance to bacterial penetration through the gown)	Disposable paper gown	Reusable cotton gown	Bacterial transmission through the paper gown material has not occurred (0 of 27 gowns). Bacterial transmission through the reusable cotton gowns occurred in 26 of 27 cloth gowns ($p < 0.001$). Authors stated that disposable paper gowns demonstrated less bacterial transmission in the laboratory with lower rates of contamination in the operating room. Authors recommended this type of disposable paper gowns for all surgical cases, especially those involving implants, because of the heightened risk of infection.
Sahu 2017 [12]	In vitro study	Gown penetration	Disposable woven polyester, disposable non-woven.	Woven cotton, polyester cotton	Disposable non-woven showed the best. Polyester and cotton showed the least resistance.

TABLE 2. Studies reporting postoperative surgical site infection in relation to the gown type

Study/Year	Design	Surgery	Infection Rate		Comments
			Single Use	Reusable	
Moylan and Kennedy 1980 [13]	Prospective/ crossover (not randomized)	Primary wound closure, including clean contaminated wounds specially in the reusable group	25/1100 (2.27%)	74/1153 (6.41%)	Significant increase in infection rate with use ofreusable gowns over disposable
Baldwin 1981 [14]	Prospective/ crossover (not randomized)	Not specified	15/3236 (1.1%)	35/3152 (0.43%)	Use of disposable draping and gowns reduced SSIs from 1.1% to 0.43% (no statistical analyses performed)
Blomgren 1983 [19]	Prospective crossover (not randomized, statistical analysis not performed)	Total hip replacement	9/27 (number of bacterial growth on the wound wash per number of procedure)	28/34	Rate of superficial SSIs was slightly higher when conventional clothing was used instead of total body exhaust suit
Garlbaldi 1984 [15]	Prospective/ randomized/blinded observer	Different elective operations. No mention of the number of clean or clean contaminated wounds	5/226 (2.2%)	6/268(2.2%)	No significant differences in SSIs between reusable and disposable gowns and drapes
Moylan 1987 [16]	Prospective/crossover	Clean and clean contaminated general surgery	30/1060 (2.83%)	73/1121 (6.51%)	Significantly higher infection rate with reusable drapes and gowns than disposable ones
Bellchambers 1996 [17]	Prospective/ randomized	Coronary artery surgery	13/250 (5.2%)	12/236(5.08%)	No differences in SSI rates in either leg or sternal wounds between reusable and disposable gown and drape systems
Belkin 1998 [18]	Prospective/ crossover/blinded observer (quasi RCT)	Different procedures with primary closure	108/2139 (5.0%)	133/2223 (6.0%)	No significant differences in SSIs between reusable and disposable gowns and drapes

The number of times garments were reused and their integrity were not part of any study outcome measures. Lengths of procedure, body mass index, antimicrobial prophylaxis, surgical scrubs and hair removal methods have all been shown to be important factors in SSIs. The type of procedure being performed is also likely to have dramatic effects on bacterial dispersal [28]. Lastly, as most of these studies are very old, many of the gown materials tested in earlier studies have undergone continuous improvements, thus the older studies may no longer be applicable. It should be mentioned that two other non-English studies [29,30], have shown that SSI rates are significantly higher with reusable cotton gowns. Yet, the evidence from these two studies remains questionable.

A review of the evidence conducted with WHO guidelines [3] based on many of the included studies in our systematic review showed with moderate and very low quality of evidence that the use of sterile disposable non-woven drapes and gowns has neither benefit nor harm compared to sterile reusable woven items. Similarly, the National Institute for Health and Clinical Excellence (NICE) in London, England, reported that there is no differences in incidences of SSIs between the use of single-use and reusable surgical drapes and gowns [31]. The NICE recommendation, therefore, was to consider the cost effectiveness of using one type of gown over the other. If the cost effectiveness is considered, one case study concluded that the use of disposable, non-woven gowns is more cost effective in prevention of SSIs, since for the single use items, direct purchase cost was the most important factor in the total cost. However, for reusable items, the most important factor was the combination of "number of reuses," "laundering and reprocessing costs" and "number of drapes used per procedure" [32]. It must be mentioned that the current European standards recommend against the further use of reusable cotton and polyester/cotton-blended drapes and surgical gowns [33] based on the available studies that showed the superiority of disposable gowns and drapes materials in reducing the bacterial contamination or SSI, although their quality of evidence was low.

In conclusion, the available low-level evidence suggests that disposable gowns have a higher ability to prevent bacterial dispersions in the OR. Regarding the incidence of SSI, the available moderate to low evidence supports that both disposable and reusable gowns have equal ability for prevention of SSIs, as long as they are sterile and fluid resistant. However, because the Level of Evidence for these studies is not high, additional randomized controlled studies are needed to examine this issue further.

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QUESTION 3: Does the use of occlusive strips at the sleeves of the surgical gowns reduce the risk of surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: There is no direct evidence that occlusive strips at the sleeves of surgical gowns reduce the risk of subsequent SSIs/PJIs. However, there is evidence that occlusive strips prevent the egress of particles from the gown-glove interface of certain gowning systems, and thereby can reduce contamination of the surgical field and potentially reduce the risks of SSIs/PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 91%, Disagree: 3%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Despite the sleeves of modern disposable gowns being repellent to liquids, the gown cuff is permeable to fluids and was recognized as a potential source of contamination to the surgical field over 60 years ago [1,2]. The failure of the gown-glove interface allows for blood and body fluids to reach the skin of the gown wearer in some circumstances [3–6].

It is, however, less well-established that the gown-glove interface is also a potential source of contamination to the patient and thus a source of subsequent PJIs/SSIs [7]. A study using 10 years of data from the New Zealand Joint Registry showed increased risk of reoperations due to infection at 6 months when surgery was performed using a surgical helmet exhaust system, although follow-up studies using multivariate analyses have refuted the latter findings [8–10]. It is postulated that one potential mechanism of contamination may be egress of particles at the gown-glove interface and that positive air pressure generated by the helmet fan may force air down the sleeve, resulting in escape of particles at gown-glove interface.

The type of gown sleeve material may also influence the ability and volume of particles that migrate out of the gown-glove junction. A study by Fraser et al. analyzing egress of fluorescent powder applied to the hands prior to gowning, compared various gowning systems (one standard gown and four surgical helmet systems), and found that all gowns had some contamination at the gown-glove interface [11]. However, one surgical helmet-gown system had significantly greater contamination ($p < 0.001$) compared to the other four, which did not differ significantly. The gowning system with the most contamination was made of a stiffer, more plasticized material that allowed for deeper folds and a less air tight seal at the gown-glove interface. Additionally, the authors noted that the stiffer sleeve material allowed for further distal migration of the glove cuff, potentially exposing the woven gown cuff. There was no statistical differences in contamination between other surgical helmet systems and the conventional gown, thereby not supporting the hypothesis that positive pressures within the suit is the main driver of contamination at the gown-glove interface for the gowns tested, but rather the gown sleeve material.

This same gown material noted to have greater contamination in the study by Fraser et al., was also tested in a similar fashion in a study by Young et al. [12]. In this study, the authors noted greater egress of fluorescent powder at the gown-glove interface with the surgical helmet system gown compared to a standard gown. An additional arm of the study included the surgical helmet system with the gown-glove junction taped and sealed with a drape tap. The addition of the drape tape eliminated the egress of particles at the gown-glove interface.

There have been some recommendations for modifications that can be made to surgical gown cuffs, that increase the security of the gown-glove interface such as making a small cut in the cuff and introducing the thumb through this hole to potentially decrease surgical contamination [13]. While this modification has been suggested there is minimal research testing this theoretical approach to decreasing the risk of SSI or PJI.

In a randomized trial, Shirley et al. found no differences in wound surgical contamination in total knee arthroplasty with the use of normal surgical gowns versus surgical helmet systems. They also showed the addition of tape at the gown-glove interface did not alter the contamination rate [14].

Although there are no studies directly linking occlusions at the gown-glove interface to a reduction in SSIs/PJIs, there is evidence that occlusions of this interface eliminates the egress of particles that may act as source of contamination, thus potentially reducing the risk of SSIs/PJIs.

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QUESTION 4: Should patients wear a mask and surgical cap in the operating room (OR) to reduce the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: Unknown. The use of face masks and surgical caps by inhabitants in the OR has not been shown to impact SSI rates, but with the limited evidence available a recommendation for or against patient usage cannot be made. Surgical cap usage by patients in the OR may decrease the risk of SSIs/PJIs by decreasing microbial air contamination.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 4%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Surgical face masks were originally developed to contain and filter droplets containing microorganisms expelled from the mouth and nasopharynx of healthcare workers during surgery. Likewise, head coverings such as surgical caps have been utilized to limit potential contamination by the shedding of hair and scalp.

The effectiveness of such strategies have been questioned in the literature. Even with the use of face masks, it has been shown that conversations in the OR increase microbial contamination [1] and that the barrier properties of face masks decreases with accumulation of moisture and venting along mask edges [2]. Additionally, it has been shown that wearing face masks decreases bacterial dispersal in front of the mouth [3], but has no effect on overall bacterial counts in the OR [4], suggesting that face masks simply redirect bacterial dispersal. On the other hand, omission of head coverings has been demonstrated to increase microbial air contamination by 3 to 5 times and increase bacterial sedimentation in the wound area 60-fold [5,6]. However, two studies have found no differences in environmental contamination with the use of head coverings [7,8].

Clinical studies have failed to demonstrate a difference in SSI rates with the use of surgical masks, while PJIs have not been specifically studied. A prospective randomized trial of 3,088 general surgery patients found no significant difference in the rates of SSIs when OR staff used a mask [9]. A prospective randomized trial of 811 patients that included orthopaedic procedures similarly found no differences in SSIs with the use of face masks by non-scrubbed staff [10]. Additionally, a meta-analysis of 3 trials and 2,113 patients found no significant difference in SSI with face mask use [11]. It is important to note that few of these trials included orthopaedic procedures and these trials had relatively high rates of SSI (3.5 to 11.5%), much higher than the current rates of SSI and PJI in total joint arthroplasty. Thus, interpretation of these findings must be made with caution.

Despite the lack of clinical evidence for the usage of face masks and surgical caps, a recommendation against patient use in the OR cannot be made for the following reasons:

1. While the evidence available shows no differences in SSIs with the use of surgical masks and caps by OR staff, no studies investigating the impact of *patients* wearing surgical masks or caps during surgery have been performed. As such, any recommendation would be extrapolation of the data from OR staff to patient usage.
2. The literature on SSI rates does not address the potential impact on non-enrolled patients having a subsequent surgical procedure in the OR that day. Particulates, such as shed hair and their impact on SSIs/PJIs on other patients have not been studied, but case order has been shown to impact risks of PJIs [12].
3. PJI has not been specifically studied as an end-point.
4. The literature does not address differential usage of masks in special populations, such as methicillin-resistant *Staphylococcus aureus* (MRSA) + nasal carriers. Eliminating mask or cap usage in these individuals may effect SSI/PJI rates.
5. Microbial contamination of air in the OR may be an underappreciated factor in the etiology of PJI [13]. Surgical cap usage in the OR may decrease the risks of SSIs/PJIs, by decreasing microbial air contamination.

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QUESTION 5: Does changing gloves during prolonged operations reduce the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs)? If so, how frequently should gloves be changed during the procedure?

RECOMMENDATION: Changing gloves intraoperatively may reduce the risks of SSIs/PJIs in arthroplasty surgery by reducing contamination. Based on prior studies, gloves should be changed after draping, before handling implants and when macroscopic perforation of the glove occurs. Gloves should also be changed at least once every 60 to 90 minutes, as contamination and glove perforation rates increase with duration of surgery.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 5%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Double-gloving is a widely-utilized technique by surgeons in many surgical subspecialties in the hopes to minimize contamination of the surgical site [1,2]. Microbiological contamination rates of gloves increases with duration of surgery, which warrants glove change during prolonged procedures [3]. However, no studies have been published that evaluate the direct relationships between changing gloves and the risks of SSIs/PJIs. Furthermore, there is conflicting evidence regarding the optimal frequency of glove changes.

Multiple studies have demonstrated that the percentage of intraoperative glove contaminations by microorganisms during total joint arthroplasty (TJA) procedures ranges from 3.4 to 30% [2,4–8]. The high variability of contamination may be attributed to differing methods of quantifying contamination. Other factors, such as ventilation in the operating room, may also impact the rates of surgical glove contamination. Most studies are observational and only reported absolute intraoperative contamination rates. These studies have not compared the differences in contamination rates between cases where gloves were changed intraoperatively, during the middle of a clean orthopaedic procedure, versus cases when they were not changed. However, in one randomized trial of 102 surgical team members, Ward et al. demonstrated that changing gloves 1 hour into a clean orthopaedic procedure was associated with significantly decreased intraoperative glove contamination rates (13 vs. 23%) [2].

There are conflicting reports regarding the optimal frequency of changing gloves during a procedure. Most studies recommend changing gloves after draping because of the high contamination rates due to disturbed laminar flow [4,7,9]. Other studies advise changing gloves before handling implants in order to prevent transfer of pathogens onto the new prostheses [2]. Regardless of contamination rates, perforated gloves are ineffective as a protective barrier against contamination [10]. Therefore, changing gloves is also recommended whenever a macroscopic glove perforation is detected, which has been shown to occur after an average of 93 ± 50 minutes of intraoperative time [11]. The recommended timing of glove changes in studies using contamination and/or perforation is variable, ranging from every 20 minutes to 90 minutes [8,11–13], also after bone resection and before inserting implants [14].

Although no studies investigate the direct link between intraoperative glove changes and SSIs/PJIs following TJA, studies from other surgical specialties demonstrate a reduction in SSIs after outer glove changes [15,16]. Due to the low PJI rates in arthroplasty surgeries, conducting a randomized control trial (RCT) with PJI as the primary outcome would be unfeasible due to the high number of surgeries needed to be performed in order for one PJI to occur. Moreover, the relevance of the findings from other surgical specialties is unclear due to the unique nature and components used in arthroplasty surgery. More studies are required to draw a definitive conclusion regarding the effectiveness of changing gloves in reducing the risk of SSIs/PJIs.

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QUESTION 6: Does shoe wear (i.e., operating room (OR) dedicated shoes, uncovered outside shoes, covered outside shoes) of the surgeon and OR staff affect the rate of surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing orthopaedic procedures?

RECOMMENDATION: There is little or no evidence to suggest that the use of dedicated OR shoes influence the rates of SSIs/PJIs. However, in view of the fact that shoes worn outside may be grossly contaminated, we recommend that outside shoes should not be worn in orthopaedic ORs, or shoe coverings should be worn to prevent the contact of outside shoes with the OR floors.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Though shoe soles are possible vectors for infectious disease, no studies currently exist directly linking shoe wear (OR only vs. outside shoes) with increased or decreased rates of SSIs/PJIs in patients undergoing orthopaedic procedures. However, published findings do suggest that OR shoes or OR over-shoes may be involved in the pathway of postoperative wound infection. In a study that assessed the level of bacterial contamination of OR shoes at the beginning and end of a working day and compared the results with outdoor footwear, findings showed the presence of pathogenic bacterial species responsible for postoperative wound infection on both shoe groups. However, outdoor shoes were the most heavily-contaminated. In addition, bacterial samples taken from OR shoes at the end of duty were less contaminated than those taken at the beginning of the day [1].

In a separate study that assessed bacterial floor colony counts in a general OR, use of OR over-shoes significantly increased colony counts, whilst non-use of over-shoes did not significantly increase colony counts [2]. However, there were no significant differences in mean bacterial floor colony counts when the two were compared. In another study that determined the effect of wearing shoe covers by medical staff and visitors on infection rates as well as the mortality and lengths-of-stay in an intensive care unit (ICU), use of shoe covers were not helpful in preventing infections of common ICU pathogens [3]. However, in the period when shoe covers were used, there were higher rates of infections compared to periods when shoe covers were not used. A study from the UK concluded that use of protective over-shoes was unnecessary for "day" surgery, which was classified as uncomplicated same-day surgical procedures, such as hernia repairs, varicose vein surgery and simple laparoscopy [4]. This poses an important question: should ambulatory versus inpatient ORs change our approach to shoe wear?

Conflicting findings have been reported. When OR floors were examined for contamination with and without the use of protective footwear, the results of the study performed by Copp et al. indicated that the use of over-shoes reduced the transfer of bacteria [5]. There is no evidence that outdoor shoes carry an increased risk of infection. However, it has been reported that the process of changing shoes or applying over-shoes can result in contamination of the hands of clinicians/surgeons [6]. In a study of 18 individuals whose hands were examined after contact with their over-shoes, findings showed that the organisms detected on their hands were likely to have been transferred from their outdoor shoes [7]. Ayliffe studied the role of the environment of the OR on postoperative wound infections. He noted that the use of surgical disinfectant mats, while proactive, may actually increase the number of organisms on the shoe soles of staff members entering the OR [8].

Based on the overall evidence, there is no evidence to support a direct link between shoe wear and the rates of SSIs and/or PJIs in patients undergoing orthopaedic surgery.

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1.14. PREVENTION: OPERATING ROOM, SURGICAL FIELD

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QUESTION 1: When should instrument trays be opened during surgery to minimize the risk of contamination?

RECOMMENDATION: Instrument trays should be opened as close to the time of surgery as possible. Once opened, trays and instruments should be covered with a sterile towel or drape when not in use.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 97%, Disagree: 2%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

The importance of airborne bacterial contamination of surgical incisions in the operating room has been appreciated for decades [1–4]. Pasquarella et al. [5] demonstrated airborne particles in the orthopaedic arthroplasty operating room (OR) to be a source of contamination for early surgical site infections (SSIs). Surgical instruments tend to be contaminated during the procedure by airborne particles and microbes, allowing surgical instruments to act as fomites even if the surgical field is not grossly contaminated [6]. Post-sterilization contamination of sets containing surgical instruments has been shown to increase the rate of deep SSIs in orthopaedic patients [7].

Airborne contamination in the OR is not constant throughout the perioperative period. Brown et al. [8] demonstrated that bacterial air counts during antiseptic preparation and draping of the patient were 4.4 times higher than during surgery, leading them to recommend opening instruments after patient preparation and draping have been completed. Chauveaux et al. [9] also noted a four-fold increase in airborne contaminants during the preparation of the limb and draping of the patient and recommended against opening of instruments until after the patient has been fully draped.

Two manuscripts clearly address the time-dependent contamination rate of orthopaedic instruments. Dalstrom et al. [10] opened trays in an OR and left the instruments exposed to the environment without an ongoing procedure, but with light traffic. They reported a time-dependent rate of contamination in opened trays, with 4% of trays contaminated by 30 minutes compared to 30% of trays contaminated after 4 hours of exposure. Trays opened and then subsequently covered with a sterile towel were protected from contamination ($p = 0.02$). Although this finding does not give a clear guideline for how long a sterile tray can be exposed to the open environment before the contamination risk becomes unacceptable (i.e., causes surgical wound infections), the authors demonstrated a direct correlation between the exposure times of open instrument trays and the risks of bacterial contamination. Coverage of the implants with a sterile towel mitigated the risk to a significant degree. Bible et al. [11] demonstrated similar protection from contamination with a sterile towel, but have contradicted the time-dependent contamination rate. Covered implants were less likely to be contaminated prior to implantation versus those that were uncovered (2 vs. 16.7%,) in their study. The simple, practical step of covering the surgical tray with a sterile towel significantly reduced the contamination risk. Therefore, no matter the expected duration of a case, implant tray coverage is a simple way to reduce the risk of contamination once a tray has been opened.

Based on the limited available data, a moderate conclusion can be made. Instrument trays should be kept in sterile packaging and opened only after the patient has been prepped and draped. Additionally, instruments should be opened as close to the time that they will be used in the procedure as possible, as there is a time-dependent contamination rate of instruments opened and exposed to the operating room environment.

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QUESTION 2: Does the use of a splash basin increase contamination of instruments and the rate of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing orthopaedic procedures?

RECOMMENDATION: Unknown. We recommend against the use of fluid-filled splash basins that sit open during surgery based upon microbiological contamination data. However, the independent association between splash basin contaminations and developments of subsequent SSIs/PJIs remain unclear.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 91%, Disagree: 4%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The use of a splash basin (a utensil filled with sterile water) in the operating room (OR) aims to provide a place to wash, store and clean surgical instruments of debris before potential reuse during an orthopaedic case. While some recommendations for surgical technologists and OR staff continue to reinforce its use [1,2], several published studies have shown evidence of bacterial contamination in these basins, with rates between 2.2 and 74.4% reported [3–8].

In a randomized controlled trial, Lindgren et al. examined the rates of positive cultures from aliquots of splash basin fluid containing either sterile water (n = 47) or a solution of 0.05% chlorhexidine (n = 53), following primary joint arthroplasties [8]. Bacterial growth in samples obtained from splash basins was 9% in the sterile water group versus 0% in the chlorhexidine solution group ($p = 0.0045$). Secondary analysis of early wound complications at six weeks following surgery revealed higher rates of SSIs in the sterile water basin group (6.4 vs. 1.9%), however this trend did not reach statistical significance ($p = 0.339$) due to inadequate statistical power.

Four prospective observational studies have also identified bacterial growth within operative splash basins [3,4,6,7]. In a consecutive series of elective orthopaedic cases, Andersson et al. showed that 13 out of 21 (61.9%) irrigation solutions stored in basins were contaminated at the end of the procedure. The colony forming units (CFUs) seen in these positive cases ranged from 8.3 to 226.5 CFUs/L with mainly *Staphylococcus epidermidis* or diphtheroid rods identified [7]. Baird et al. revealed a contamination rate of 74.4% in specimens sampled from splash basin fluids after randomly-selected orthopaedic procedures (n = 78). In their series, 59% of the positive fluid cultures had polymicrobial signal and 12% showed counts of > 100 CFU/100 ml [4]. Similarly, Anto et al. demonstrated a 23.8% rate of bacterial contamination in liquid samples removed from splash basins [3]. The mean number of instruments placed within the basin was 46 (range 12 to 74). Coagulase-negative staphylococci were found to be the most common contaminating organism. No patients with contaminated samples developed features of superficial or deep surgical site infection at the minimum six-month follow-up in their series.

In contrast, Glait et al. found lower rates of bacterial contamination in samples taken from splash basins that were used to wash and store instruments in a series of 46 primary hip or knee arthroplasty cases. Only 1 case out of 46 (2.2%) tested positive for bacterial growth [5]. However, this study used a single swab of the basin for culture testing as opposed to the basin fluid aliquots used in all other studies, which make account for their conflicting observations. Furthermore, in a larger series of 87 TJAs using swabs placed in transport mediums prior to culture, Jonsson et al. showed that splash basins were the most commonly contaminated site. They found that 12 of 87 basin swabs (24.1%) tested positive on culture. Again, intraoperative contamination could not be correlated to clinical infections on long-term follow-up. The authors posit that a larger study group with multivariate analysis may be able to define this independent effect of intraoperative contamination [6].

In further contrast to the wider body of literature suggesting basins are a possible source of contamination, surgical technologists have often been trained to use these basins as a means of instrument decontamination and thus may still encourage their use in the OR [1]. The Association of Surgical Technologists recommends that "a basin of sterile water should be available in the sterile field for the soaking and cleaning of instruments" [1]. In addition, Beauclair et al. recently suggested the importance of using a sterile water basin for "moisturization and removal of bioburden from reusable surgical instruments" [2]. The Association of Perioperative Registered Nurses along and Association of Surgical Technologists have also previously recommended the use of a splash basin to keep reusable instruments clean and moist after wiping them down [2]. However, these recommendations are largely in contrast to multiple reports regarding the culture contamination seen in splash basins.

In summary, several studies have confirmed positive bacterial growth of the fluid from the operative splash basin [3–8], and suggest that this may be a source of intraoperative contamination. However, conclusions regarding the direct association between intraoperative contamination in splash basins and subsequent SSIs/PJIs remain unclear [6]. Nevertheless, in the fight against orthopaedic infections, every possible source of bacterial contamination should be eliminated [9]. We, therefore, advocate that splash basins should be abandoned from the OR until more evidence is available.

Isolated reports also suggest that filling splash basins with a dilute antiseptic solution such as chlorhexidine gluconate or dilute betadine, rather than sterile water, may have a role in reducing rates of microbial contamination in basins [8,10,11].

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QUESTION 3: Does changing the electrocautery tip during surgery reduce the rate of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: While it is clear that electrocautery tips may become contaminated during surgery, no study has been able to prove a relationship between the amount of time that an electrocautery tip is exposed and its contamination. However, in cases where there is known infection, such as a one-stage or two-stage exchange arthroplasty for PJI, we do recommend changing the electrocautery tip at the end of the "dirty" portion of the procedure and prior to reimplantation of components.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 5%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Aseptic techniques are fundamental to the prevention of SSIs and PJIs. It is well-known that sterile surgical equipment can be contaminated intraoperatively, including gloves, gowns, light handles and even instruments that are introduced directly into the wound, such as suction catheter tips [1–6]. Certain recommendations have even been put forth regarding surgical equipment that have the potential to contaminate the surgical site, such as suction tips [7].

Electrocautery is frequently utilized during orthopaedic procedures for soft tissue dissection and obtaining hemostasis. Contamination of electrocautery tips was first noted in the dermatology literature. *Staphylococcus aureus* was shown to transfer from tissue to sterile tips and vice versa [8]. Shahi et al. performed the first study, examining the contamination of electrocautery tips in orthopaedic surgeries [9]. Electrocautery tips were collected from 25 primary total hip arthroplasties (THAs) and 25 aseptic revision THAs and were inoculated in cultures. Five unused electrocautery tips were also inoculated into cultures as negative controls. Cultures isolated an organism in 4% of electrocautery tips from primary THAs and 8% of tips from aseptic revision THAs. No organisms were isolated from the unused and clean tips. Thus, the rate of positive cultures was twice as high in the revision THA group [9].

While revision THA is known to take longer than primary THA, there was no association between electrocautery tip exposure time and contamination rate in the latter study. Conversely, a similar study conducted by Abdelaziz et al. looking at both primary and revision hip and knee arthroplasties, revealed a higher rate of electrocautery tip contamination in their primary arthroplasty cohort [10]. In this study, the authors reported a 10% rate of electrocautery tip contamination for the primary arthroplasty group and 4% for the aseptic revision cohort. All negative controls in this study also failed to isolate an organism on culture. This study also failed to show an association between duration of exposure of the electrocautery tip and subsequent contamination [10]. Furthermore, they noted a high rate of contamination (15/50, 30%) of the electrocautery tips in septic revisions.

In conclusion, electrocautery tips are vulnerable to contamination during surgery. However, the importance of such contamination is questionable. Larger, adequately-powered studies with sufficient follow-up to determine if this contamination is a source of subsequent SSIs/PJIs are needed but may be difficult to perform due to the large sample sizes needed for adequately powered SSIs/PJIs samples. Given the high rates of contamination noted during septic cases, changing the electrocautery tips prior to implantation of components is recommended.

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QUESTION 4: Should suction tips be regularly changed during surgery? If so, how frequently?

RECOMMENDATION: Yes. The suction tips should be regularly changed during surgery. Although no time threshold has been established for its exchange, we believe it should be changed every 60 minutes. Studies have shown that suction tips get contaminated during surgery and the contamination rate is higher with prolonged operative time.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 85%, Disagree: 9%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Contamination of the suction tip during surgical procedures has been reported [1–7]. This occurs either by airborne bacteria because of the large volume of air passing through the suction tip, by direct contamination of the tip by contact with patient's skin or by improper handling by operating team members. In the orthopaedic field, several studies reported contamination rates of suction tips as high as 37 to 65% in conventional/non-laminar air operating theaters [4,6–8] and 4.6 to 41% in ultra-clean/laminar flow operating theaters [2,5]. *Staphylococcus* species (coagulase-negative and epidermidis) were the dominating contaminants isolated from suction tips, comprising 34 to 100% of cases [1,2,4–8] .

Only one study, by Givissis et al., reported a patient that developed a deep wound infection with the same microorganism responsible for contaminating the suction catheter tip [4]. No other study was identified showing an association between contamination and deep or superficial infection. Furthermore, two studies showed relationships between the duration of use, and the contamination rates of suction tips. Greenough et al. [6] reported a 37% (11/30) contamination rate after a median of 82 minutes of operating time (suction usage), compared to a 3.3% (1/30) rate after a median duration of 17 minutes of suction usage. Givissis et al. [4] showed that in surgeries lasting less than 1 hour, suction tip cultures were positive only in 1 out of 11 (9.1%), compared to 26 out of 39 (66.7%) when surgery operative times exceeded 1 hour.

When analyzing studies from different surgical fields, considerably greater contamination of suction tips was also noted. Laham et al. [9] analyzed general contamination in public and private general operating rooms and observed suction tip contamination in 13.33% of cases. Larson et al. [10] evaluated suction catheter contamination during aortic valve replacement surgery and showed contamination rates from 48 to 52%. McMaster et al. [11] found a contamination rate 21% of suction tips used in Cesarean deliveries. In non-orthopaedic surgery, main contaminants isolated from suction tips were also *Staphylococcus* species (coagulase-negative) comprising up to 76% of cases [9,10].

Multiple authors recommend changing the suction tip/catheter during prolonged surgeries or before critical steps of surgery (preparing femoral canal or cementing components) and turning off the suction when it is not in use [2–7,12]. However, there are concerns that turning off the suction might impose risk of contaminations of the surgical field due to backflow of the material along the suction tube and tip. Therefore, we think that suction device should be turned on as late as possible to minimize the risk of airborne contamination. Because of the high contamination rates and plausible bacterial seeding to operating wound, use of suction tips as a probe, retractor or pointer during surgery should be actively discouraged.

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QUESTION 5: Should suction tips enter the intramedullary canal during orthopaedic surgery?

RECOMMENDATION: Suction tips can be introduced into the intramedullary canal during orthopaedic surgery to remove fluid as needed, but should not be left in the canal where they draw in large volumes of ambient air and particles that could potentially contaminate the intramedullary canal.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 91%, Disagree: 4%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

It has been suggested that the suction catheter tip may be contaminated and act as a reservoir for microorganisms [1,2]. As such, contact between the suction tip and any area of the surgical field is likely to lead to contamination and serve as a nidus for later infections. Unnecessarily keeping the suction catheter in the intramedullary canal can draw ambient air into the intramedullary canal, where it can deposit bacteria and increase the risk of subsequent infection. However, there are no studies to support this theoretical concern and one may never expect to obtain or generate real-world clinical data to examine this issue.

Greenough et al. [3] found a 37% rate of contaminated operative suction tips used in total hip arthroplasties (THAs). However, when evaluating the suction tips used only for cleaning the femoral shaft, only one of 31 suction tips were contaminated. As such, the authors advised changing the suction tip before preparing the femur in THA. The same conclusion was drawn by Robinson et al. [1] who conducted a similar study among patients undergoing THA and identified a 41% contamination rate of suction tips. Insull et al. [4] presented a lower rate of contamination of 7.8%, but the authors did not report on the use of the suction tip in the intramedullary canal.

Strange-Vognsen et al. [5] reported a contamination rate of 54% for suction tips used for THA. However, among the 12 culture-positive suction tips, 9 grew coagulase-negative staphylococci, which is a common culture contaminant [6]. Therefore, it is possible that a significant number of the culture-positive suction tips could represent false-positive results. The authors advised that the suction be turned on only when in use, however, there are concerns of backflow of suction container content when turned off [7].

Givissis et al., [8] studied 50 patients who underwent trauma procedures during which suction was used and found contaminated suction tips in 27 cases (54%). The duration of the operative procedure appeared to be an important variable influencing suction tip catheter contamination. The tip was contaminated in only 1 out of 11 procedures lasting less than 1 hour (9.1%), as compared to 26 out of 39 (66.7%) when operative times exceeded 1 hour. However, deep wound infection was recorded in only one case. It appears that operative lengths of more than one hour increases the risk of suction catheter contamination, raising it seven-fold from 9.1 to 66.7%.

When assessing the clinical relevance of these studies, it is important to know that contamination of a suction catheter tip at the completion of surgical procedure does not necessarily equate to infection [8]. As such, there is lack of evidence addressing the issue of suction tip contamination and subsequent infection. There is little data related to the influence of using the suction tip inside the medullary canal and the potential for subsequent infection.

In the absence of conclusive evidence, drawing on the data that shows suction tips are contaminated in a large number of cases lasting more than one hour, we recommend that suction tips not be inserted into the medullary canal except for removal of blood and to obtain the necessary visualization. Efforts should be made not to leave the suction tip inside the medullary canal, as this carries the theoretical risk of introducing ambient air and particulate bacteria into the canal.

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1.15. PREVENTION: ANTISEPTIC IRRIGATION SOLUTION

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QUESTION 1: What antiseptics can be used to prevent biofilm formation?

RECOMMENDATION: Although several studies have demonstrated the ability of certain antiseptic agents to prevent biofilm formation in vitro, the ability of antiseptics to provide prevention of biofilm formation in vivo is uncertain. They may have utility in the context of revision surgery due to existing infection, but this issue has not been adequately studied.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

It has not been established whether a specific antiseptic or a combination of agents is better to eradicate biofilms from an implant surface in vivo [1]. So far, almost all of the studies focused on the abilities of antiseptics to inhibit biofilm formation have been demonstrated in in vitro studies [2–5].

Santos et al. performed a crossover, randomized double-blind clinical trial to evaluate the effects of two chlorhexidine solutions (alcohol-containing 0.12% chlorhexidine solution and alcohol-free 0.12% chlorhexidine solution) against supra- and sub-gingival biofilm formation. The group found that both solutions had similar inhibitory effects on the formation of biofilms [6]. In addition, Quintas et al. performed an observer-masked, crossover, randomized clinical trial to evaluate the in situ antiplaque effect after four days of using two commercial antimicrobial agents (essential oils and 0.2% chlorhexidine) in the short-term on undisturbed plaque-like biofilm [7]. Although the 0.2% chlorhexidine showed better results with regard to reducing the thickness and covering grade by the biofilm, both antiseptics had high and similar antiplaque effects.

The ability of acetic acid and polyhexanide to prevent biofilm formation has also been mentioned in the literature. Halstead et al. demonstrated that acetic acid at low concentrations of 0.16 to 0.31% was able to inhibit biofilm formation in vitro [8]. Lenselink et al. performed a cohort study to evaluate the clinical efficacy of the polyhexanide-containing bio cellulose dressing for the eradication of biofilms in non-healing wounds [9]. They suggested that continuous application of polyhexanide, using a bio cellulose wound dressing, reduced biofilm in the stagnating wounds treated, thus promoting healing.

Regarding the clinical use of povidone-iodine to prevent the formation of biofilms, there are limited studies in vitro. Hill et al. utilized a sophisticated in vitro biofilm model that was designed to closely mimic chronic wound biofilms and demonstrated the complete destruction of an established seven-day mixed Pseudomonas and *Staphylococcus* biofilm by iodine-based dressings [10]. Kanno et al. suggested that irrigation of wounds with 1% povidone-iodine was an effective way to reduce bacterial counts on the wound surface and prevent new biofilm formation by using a rat model of wound chronic biofilm infection [11]. However, Presterl et al. found that povidone-iodine was inferior to hydrogen peroxide and alcohol for the eradication of *Staphylococcus epidermidis* biofilms [12].

It is worth noting that many biofilm infections occur much later in the postoperative period, often due to the hematogenous dissemination of bacteria to the site of an implanted device from a breach in surface structures [13]. Indeed, this can occur months or even years after implantation and it is unlikely to prevent this mode of infection development with the use of antiseptic agents at the time of perioperative period. The role of antiseptics in various debridement protocols for the treatment of established periprosthetic joint infections (PJIs) remains controversial. Each clinical scenario is unique in terms of causative pathogen, host factors, local tissue viability, as well as the duration and virulence of the infection. If the surgeon is attempting to salvage the existing prosthesis through a debridement, antibiotics and implant retention (DAIR) protocol, it is imperative that all biofilm should be removed through mechanical and chemical disruption [14–16]. If a one-stage revision including component explantation, debridement and reimplantation of a new prosthesis is to be undertaken in a single surgical setting, the importance of debriding all infected tissue is vital. The role of antiseptics, in this case, is not to treat existing biofilm, as all prosthetic components will have been removed. Instead, the purpose is to aggressively treat the remaining bone and its soft tissue envelope to prevent recolonization. Antiseptics used for this purpose include acetic acid, Dakins solution (NaOCl), povidine-iodine and hydrogen peroxide [17]. In this situation, the volume of antiseptic solution may be more important than the combination and sequence of agents [17,18].

The use of antiseptic agents during the perioperative period has the potential to reduce the rate of surgical infection early in the postoperative period. Additionally, the use of certain antiseptic solutions for lavage, during primary and revision total joint arthroplasty operations, has the potential to reduce infection rates [19]. However, validated protocols do not exist for the use of such solutions in terms of concentration, volume and duration of exposure. More in vivo studies are needed to evaluate the use of various antiseptic agents for this purpose, such that direct comparisons between agents can be made.

Ultimately, although several studies have demonstrated the ability of certain antiseptic agents to prevent biofilm formation in vitro, the ability of antiseptics to provide protection against biofilm formation in vivo is uncertain. They may have utility in the context of revision surgery due to existing infection, but this issue has not been adequately studied.

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QUESTION 2: What is the optimal irrigation solution (i.e., type, volume, frequency) to be used during clean elective orthopaedic procedures?

RECOMMENDATION: There is ample evidence to support the World Health Organization's (WHO) and Centers for Disease Control and Prevention's (CDC) recommendations that advocate the use of dilute betadine for the irrigation of wounds during surgical procedures. The optimal volume of irrigation solution is not known.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 75%, Disagree: 16%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

Intraoperative irrigation during clean elective orthopaedic procedures is one aspect of the operative protocol to reduce surgical site infections (SSIs), and there is general consensus that this technique in some form should be performed. Recently released guidelines by the CDC and WHO recommend intraoperative irrigation with dilute betadine prior to closure [1,2]. Betadine contains aqueous iodophor in the form of povidone-iodine which becomes chemically toxic to microorganisms when released as free iodine [3,4].

Povidone-iodine irrigation initially garnered support from studies in other fields, such as general, urologic, cardiovascular and spine surgeries [5–14]. A meta-analysis of seven randomized control trials demonstrated a statistically significant benefit for incisional wound irrigation with aqueous betadine, compared to normal saline solution (odds ratio (OR): 0.31, p = 0.007) [2]. In a larger meta-analysis of 15 level I or II studies in various surgical fields, 10 studies demonstrated that povidone-iodine irrigation was more effective than the control method that included irrigation with saline, water or no irrigation [15].

Although well-studied in other specialties, only one retrospective cohort study addresses intraoperative betadine irrigation in primary joint arthroplasty [16]. Brown et al. demonstrated a statistically significant reduction in SSI from 0.97 to 0.15% with the use of 0.35% povidone-iodine. Kokavec et al. studied betadine irrigation in a pediatric population undergoing surgery on the proximal femur, hip and pelvis [7]. In this study, two superficial wound infections were identified in the non-betadine group (2/73, 2.7%) and no infections were identified in the betadine group (0/89, 0%). (Table 1).

In addition to isotonic saline and ringers lactate, several solutions such as antiseptics and antibiotic solutions have also been proposed as potential irrigation fluids in orthopaedic surgery. However, there is no consensus on a gold standard because of lack of clinical studies on the topic. Chlorhexidine is an antiseptic that alters the osmotic equilibrium of bacterial cells by binding to negatively charged molecules on the cell wall [17,18]. Chlorhexidine has a broad spectrum of activity [19] and can be bacteriostatic or bactericidal depending on its concentration [20]. Frisch et al. compared 0.05% chlorhexidine to normal saline irrigation in total knee arthroplasty (TKA) and 0.05% chlorhexidine to < 2% dilute betadine in total hip arthroplasty (THA) [21]. There was no significant difference in the rate of superficial or deep SSI between groups, which suggest that chlorhexidine may be comparable to normal saline in reducing infection rates.

While there is some evidence for the optimal irrigation solution, few studies have demonstrated an optimal volume or method for performing irrigation [22,23]. Additionally, there is little support for the benefits of adding antibiotics to irrigation solution, which was

TABLE 1. Summary of orthopaedic literature comparing the efficacy of irrigation solutions with respect to prevention of SSI

Author	Category	N	Intervention	Comparison	Study Design	Analysis	Outcome	Incidence of SSI	P Value
Brown	TJA	2,550 (1,862 pre/ 688 post)	Betadine	Saline	Retrospective, pre-post	Univariate	D	0.15% vs. 0.97%	0.04
Cheng	Spine	414 (206 Ccrl/208 intervention)	Betadine	Saline	RCT	Multivariate	S & D	0% vs. 3.4%	0.01
Chang	Spine	244 (124 ctrl/120 intervention)	Betadine	Saline	RCT	Univariate	S & D	0% vs. 4.8%	0.03
Kokavec	Ortho	162 (73 ctrl/89 intervention)	Betadine	Saline	RCT	NA	S	0% vs. 2.7%	NA
Frisch	THA	391 (253 pre/ 138 post)	Chlorhexidine	Betadine	Retrospective, pre-post	Multivariate	S & D	(S) 0% vs. 1.2%	0.56
								(D) 0.8% vs. 1.6%	0.30
Frisch	TKA	659 (411 pre/ 138 post)	Chlorhexidine	Saline	Retrospective; pre-post	Multivariate	S & D	(S) 0.8% vs. 0.7%	0.91
								(D) 1.2% vs. 0.7%	0.53

S, superficial infections; D, deep infections

shown to be ineffective on metal surfaces in vitro, and thus this practice is not currently recommended by the WHO [22,24]. However, a single surgeon has reported beneficial results when vancomycin and polymyxin was added to irrigation solution in 2,293 TJAs [25].

Overwhelming evidence from published randomized control trials (RCTs) on the use of irrigation solutions for clean, elective orthopaedic procedures or surgeries suggest that both normal isotonic saline and ringers lactate solutions are safe and effective irrigation fluids. However, the majority of these studies were based on shoulder arthroscopic surgery [26–32], with limited studies on TKAs [31,33,34]. Whether ringers lactate is better than normal saline or vice versa is not known. However, in a laboratory-based study on surgically resected menisci from patients who underwent arthroscopic knee surgery, investigators aimed to determine whether there was a difference in the effect on cell morphology and function between isotonic saline and ringers lactate solutions. The findings showed that ringers lactate maintained better meniscal cell integrity compared with isotonic saline [35].

Emerging and consistent evidence suggests that warming of irrigation fluids (whether normal isotonic saline or ringers lactate) to temperatures of 32 to 40°C compared with room temperature irrigation fluids, decrease the risk of perioperative hypothermia and reduces inflammatory response in patients undergoing shoulder, hip or knee arthroscopy [28,31,36–38]. Only two RCTs have, to our knowledge, reported that warmed irrigation fluids were not superior to room temperature fluids in reducing the occurrence of perioperative hypothermia [30,39].

Results from three RCTs provided evidence that the addition of epinephrine to irrigation fluids improved the clarity of the visual field of surgery, reduced intraoperative bleeding and reduced total operating time compared with plain irrigation fluids [27,29,32]. The benefits of using chilled irrigation solutions in orthopaedic procedures was uncertain until recently. Li and colleagues performed an RCT and compared the effects of continuous irrigation of 4,000 mL cold saline plus 0.5% epinephrine vs. 4,000 mL normal saline at room temperature in patients undergoing TKAs [33]. Irrigation with cold saline was demonstrated to be associated with decreased postoperative pain, reduced intraoperative blood loss and improved quality of life.

Though commonly-used isotonic solutions such as normal saline or ringers lactate have been reported to be safe for joint irrigation in orthopaedic procedures, rare adverse events from excessive fluid irrigation have been documented. It has been reported that hyperosmolar solutions may have the potential to minimize these problems. However, their benefits have only so far been demonstrated in animal models. In a recent RCT, hyperosmolar irrigation was shown to decrease periarticular fluid retention in shoulder arthroscopy compared with standard of care irrigation fluid [26].

The role of continuous irrigation or pulse lavage in orthopaedic surgery has progressed from open fractures and contaminated wounds to being used in clean elective procedures. Furthermore, the optimum volume of irrigation solution used during orthopaedic procedures varies from one surgery to another. In studies of patients undergoing shoulder arthroscopy, average volume of fluid used for irrigation ranged from 3.7 to 11.4 L, and this was based on continuous irrigation with a pressure-control pump maintained at pressure settings of 30 to 60 mmHg [26–32].

For hip arthroscopy, evidence was based on an observational prospective study [38]. Median volume of irrigation solution was 27 L using an infusion pump with pressure between 45 and 65 mmHg.

In the RCT by Kelly et al. investigating patients undergoing knee arthroscopy, the average volume of irrigation fluid used was 11.7 L [39]. In two studies of TKA (one RCT and one case series), continuous irrigation with 4 L of normal saline solution was used during surgery in each study [33,34]. In an RCT of hip hemiarthroplasty, 2 L of normal saline administered by pulse lavage was associated with a 30-day lower infection rate compared to 2 L normal saline washout by jug or syringe [10]. No data was reported on the pressure settings of the infusion pump in these studies.

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QUESTION 3: Does the pressure of the pulsatile delivery mechanism for irrigation fluid influence the efficacy of the irrigation solution to eradicate infecting organisms in the wound?

RECOMMENDATION: A series of clinical studies have been unable to observe differences in clinical outcomes or reoperation rates between high-pressure vs. low-pressure wound irrigation. Tangential hydrosurgery is an emerging irrigation method that, though promising, still requires further investigation.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 90%, Disagree: 4%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

There has been a combination of in vitro models, animal models and clinical studies that have investigated the efficacy of irrigation pressure in wounds. The majority of the in vitro and in vivo studies have been completed in regards to traumatic wound debridement. These studies have looked at the ability of irrigation methods to remove bacteria, inorganic contaminate, tissue damage induced from irrigation and possible differences in distribution of contaminate in the wound after irrigation. A series of clinical studies have been completed that do not demonstrate any difference in clinical efficacy between high-pressure and low-pressure irrigation.

High and low-pressure lavage has mixed results in removing contaminants from the wound. In vitro studies have shown an increased ability of pulsatile lavage to remove inorganic debris [1,2] and bacteria [3]. Animal models have had indeterminate results. In a rabbit animal model, high-pressure irrigation and bulb syringe irrigation were equally as effective at removing debris. In an animal model using bioluminescent bacteria, high-pressure lavage demonstrated an increased ability to remove bacteria [4].

Concerns have been raised that high-pressure irrigation may distribute contaminates deeper into soft tissues. Paradoxical results that high-pressure irrigations have fewer contaminants removed support these results [5,6]. This data is supported by luminescent bacteria in wound animal models where high-pressure irrigation has improved or has an equivalent ability to initially remove bacteria, but that there is a higher rebound of bacteria several hours after completion of the procedure [7]. In an in vitro model of a contaminated human tibial fracture, high-pressure pulsatile lavage followed by cultures of serial sections at increasing distance from the fracture site revealed a reproducible pattern of bacterial propagation into the intramedullary canal [8]. In addition, bone destruction was found to vary proportionally with the depth into the canal.

There have been a large number of in vitro studies demonstrating possible increased levels of microscopic and macroscopic bone and tissue destruction after high-pressure pulse lavage as compared to low-pressure irrigation. On bone specimens, high-pressure pulse lavage was associated with more fissures and defects in cancellous bone [3], bone structure and fracture healing [3,9]. Similar results have been seen with high-pressure irrigation having increased gross damage to soft tissue as compared to low-pressure irrigation [1,5,10]. These results show that high-pressure pulsatile lavage penetrates and disrupts soft tissue to a deeper level than low-pressure lavage, causing considerable gross and microscopic tissue disruption [5].

Animal models support the findings from these in vitro models. High-pressure lavage can inhibit early new bone formation in an intraarticular fracture rabbit model. There was a direct relationship between irrigation pressures and the amount of cellular materials removed from the trabeculae at the irrigation site [11]. Animal models have shown that high-pressure pulsatile lavage of musculoskeletal wounds can cause injury to tissue, resulting in myonecrosis and dystrophic calcification [12]. High-pressure pulsatile lavage has also been shown to significantly decrease the mechanical strength of fracture callus (peak bending force and stiffness) during the early phases of healing (three weeks), as compared to bulb syringe techniques in a non-contaminated diaphyseal femoral fracture model in rats [13].

Multiple clinical studies have demonstrated that high or low-irrigation pressure results in similar clinical outcomes. The largest of these was the Fluid Lavage of Open Wounds (FLOW) study [14]. This was a large, well-designed, prospective, randomized, two-by-three factorial design clinical study comparing three irrigation pressures and two irrigation solutions (normal saline and castile soap). A total of 2,551 patients were enrolled and the primary end-points were reoperation within 12 months from the index procedure or treatment of a wound infection. The FLOW study demonstrated that the rates of reoperation were similar regardless of irrigation pressure (ClinicalTrials.gov NCT00788398) [14].

These findings are supported by several smaller studies. The FLOW study design was based on pilot data that suggested that low pressure irrigation of open wounds may decrease reoperation rates for infection, although the pilot study did not observe any statistically significant differences between high and low pressure irrigation groups (ClinicalTrials.gov NCT01069315) [15]. In a small prospective randomized clinical study of acute periprosthetic joint infection, there were no differences seen with the use of high versus low-pressure irrigation with outcomes defined by retention of prosthesis or elevation of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) at one year [16].

Irrigation pressures may have difficulty removing bacteria from the wound because biofilm acts as a viscous fluid. Biofilms are viscoelastic and resist detachment from increased fluid flow and shear by deformation. This allows the biofilm to remain attached to the surface, or roll along a surface in response to a shear stress from fluid [17]. Given this limitation of pulsatile irrigation as well as the concerns for bone destruction discussed above, there has been a recent interest in exploring novel delivery mechanisms of the irrigation fluid. In a prospective randomized control study, tangential hydrosurgery was compared to standard surgical debridement of grade IIIA and IIIB open tibia fractures in 40 patients. It was found that when hydrosurgery was used, significantly fewer debridement procedures were required prior to final wound closure [18]. Hydrosurgery debridement was also evaluated as a method for removing bacteria from fracture implants. Specifically, when comparing the use of hydrosurgery, pressurized pulsatile lavage and bulb syringe to deliver the same volume of saline to debride *Staphylococcus aureus*-contaminated stainless-steel fracture plates, residual bacterial loads were found to be significantly lower in the hydrosurgery group [19].

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QUESTION 4: Does the addition of topical antibiotics (polymyxin and/or bacitracin) to irrigation solution offer additional antibacterial properties?

RECOMMENDATION: Guidelines from the World Health Organization (WHO) and National Institute for Health and Clinical Excellence (NICE) advise against the addition of topical antibiotics to irrigation solutions. Recent Centers for Disease Control and Prevention (CDC) recommendations suggest an uncertain trade-off between the benefits and risks of intraoperative antimicrobial irrigation for the prevention of surgical site infections (SSIs). While data regarding the antimicrobial efficacy of irrigation solutions containing antibiotics, such as polymyxin-bacitracin is conflicting and largely based on non-orthopaedic studies, we advocate against its intraoperative usage in the face of growing antimicrobial resistance concerns, costs and hypersensitivity implications.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 4%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

While the intraoperative use of irrigation solutions is an important strategy for mitigation of SSIs and periprosthetic joint infections (PJIs) in patients undergoing orthopaedic procedures [1–3], the optimal irrigation solution remains unknown. Surgeons worldwide continue to add topical antibiotics to irrigation fluid [4], assuming that this solution has local activity that can help eliminate bacteria. However, published literature suggests that the addition of antibiotics to irrigation confers no added benefits [5–7], and may even be deleterious [7–9].

Two clinical practice guidelines issued by the WHO and NICE advise that antibiotic incisional wound irrigation before closure should not be used for the purposes of preventing SSIs, although these were based on generally low-quality evidence [10–12,5]. Furthermore, using available data from five randomized controlled trials [13–17], the CDC concluded that antibiotic irrigation of the incisional wound conferred neither benefits nor harms in reducing SSIs when compared to no irrigation or saline irrigation [12]. Additionally, the WHO guideline development group highlighted the risks of emergence of antimicrobial resistance (AMR) with the use of antibiotics for wound irrigation.

Moreover, in vitro studies have raised concerns about the bactericidal efficacy of adding antimicrobials to irrigation fluids [18,19]. Anglen et al. found that the addition of antibiotic drugs (including bacitracin and polymyxin/neomyxin) to irrigation solutions had no significant effects on bacterial removal. None of the antibiotic solutions tested were statistically different from saline alone in the amount of bacteria removed from a *Staphylococcus*-coated stainless steel screw model [18]. In a series of breakpoint experiments, Goswami et al. showed polymyxin-bacitracin solution was significantly less efficacious ($p < 0.001$) in eradicating *S. aureus* versus other tested irrigation solutions, including 0.3% povidone-iodine, 0.05% chlorhexidine and 0.125% sodium hypochlorite [19]. Similarly, using a rat model of a contaminated paravertebral wound containing a wire implant, Conroy et al. found no significant benefit with respect to

the rates of positive wound cultures following bacitracin-antibiotic irrigation over normal saline [20].

In addition to the questionable efficacy and perpetuating AMR, concerns have been raised about the harmful effects on wound healing of bacitracin-containing irrigation solutions, as have been reported in a prospective randomized clinical trial [7]. The study recruited 400 patients with a lower extremity open fracture who received irrigation with either a bacitracin antibiotic solution or a nonsterile castile soap solution. No differences in infection rates were seen between the two study arms ($p = 0.2$), but wound healing problems were found to be significantly higher in the bacitracin group (9.5% vs. 4%, $p = 0.03$).

An increased risk of hypersensitivity and the potential for anaphylactic reactions have also been cited [7–9]. Bacitracin is a polypeptide antibiotic effective against a variety of gram-positive bacteria and its pharmacological activity is exerted by the inhibition of prokaryotic cell-wall synthesis. Polymyxins are a group of cyclic non-ribosomal polypeptide antibiotics that have gram-negative activity. Studies have reported that these antibiotics may produce serious systemic effects. Damm et al. reported three cases with a severe anaphylactic reaction after prophylactic bacitracin irrigation in the setting of pacemaker insertion [21]. Similarly, Antevil et al. attributed the use of bacitracin irrigation to anaphylactic shock during a case of revision total knee arthroplasty (TKA) [8]. Furthermore, in a multi-institutional study by the North American Contact Dermatitis Group involving patients with suspected allergic contact dermatitis, bacitracin was noted as the sixth most common allergen with 9.2% positive on patch testing [22].

Efficacy data from largely historical studies suggests some utility for polymyxin-bacitracin irrigation. Savitz et al. investigated the addition of polymyxin-bacitracin to saline lavage in 50 spinal procedures [23]. They reported that the incidence of bacterial growth reduced from 64 to 4% with the addition of antibiotics to irrigation and no wound infections were reported in postoperative phase. Similarly, in 1972, Scherr et al. showed a significant in vitro decrease in local bacterial concentrations after topical administration of bacitracin and other antimicrobials [24]. Rosenstein et al. also showed that irrigation with 50 mL of bacitracin solution into the intramedullary canal of canine femora inoculated with staphylococci decreased the number of positive cultures one week later [25]. A single surgeon series also reported beneficial results when vancomycin and polymyxin were added to irrigation solution in 2,293 total joint arthroplasties (TJA) [26]. Despite these reports, data within the orthopaedic literature remains unconvincing due to poor study design or limitations with defining appropriate endpoints for efficacy in musculoskeletal wounds [9].

More recent data from five non-othopaedic randomized control trials compared irrigation of the incisional wound with an antibiotic solution to irrigation with normal saline or no irrigation showed limited efficacy [13–17]. A meta-analysis of these trials demonstrated no significant differences between antibiotic irrigation and no irrigation or irrigation with only saline solution (odds ratio (OR): 1.16, 95% confidence interval (CI) 0.64 to 2.12, $p = 0.63$). The overall quality of evidence in this meta-analysis was cited as low, however, due to the risk of bias and imprecision [6].

While the cost-effectiveness of polymyxin-bacitracin has not been formally evaluated, 1 operative orthopaedic procedure typically uses 150,000 units of bacitracin (50,000 units per liter of saline), which adds a cost of $150.00 according to estimates by Anglen et al. [9].

In conclusion, two clinical practice guidelines based on a review of the evidence, recommend against antimicrobial wound irrigation to reduce the risk of SSIs [5,10,11]. The efficacy of irrigation solutions with supplemental topical antibiotics in orthopaedic procedures remains controversial due to the paucity of available evidence. Future well-designed randomized controlled trials using current standard of care protocols for SSI prevention are needed to evaluate commonly used irrigation practices with a special emphasis on the agents used and a focus on orthopaedic procedures [26,27]. Trials should also address cost-effectiveness and adverse events associated with the agents used for irrigation. In the interim, given the lack of proven efficacy and the potential for harm, we advise against the addition of topical antibiotics to irrigation solution.

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QUESTION 5: Is there a role for non-antibiotic natural antiseptic agents (e.g., honey, vinegar) as an irrigation solution during surgical debridement for periprosthetic joint infections (PJIs)?

RECOMMENDATION: There may be a role for non-antibiotic antiseptic agents (e.g., honey, vinegar, etc.) as an irrigation solution during surgical debridement.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 39%, Disagree: 43%, Abstain: 18% (NO Consensus)

RATIONALE

As multi-antibiotic resistant organisms become more prevalent, the need for non-antibiotic anti-microbial therapy becomes important again (as it was in the pre-antibiotic era). Several options are readily-available for use as a local chemical debriding agent for local irrigation of PJI wounds after surgical and mechanical debridement has been completed [1]. Among these options are vinegar (acetic acid), honey, hydrogen peroxide, local anesthetic, iodine and chlorhexidine. There are no randomized control trials of deep wound irrigation using any of these substances in PJIs. The evidence is limited and often inferred from chronic wound management [2,3].

Vinegar

Vinegar has been in use for millennia as an antibacterial agent [4]. The only case series reporting its use as a deep wound irrigant in orthopaedics was by Williams et al. in 2015 [5]. This study showed that the use of 3% acetic acid (AA) soak, as part of a debridement protocol, was safe in patients. While the exact mechanism of action is yet to be determined, AA concentrations as low as 0.19% vol/vol in vitro are sufficient to completely inhibit bacterial growth. It is postulated that pH change is a potential mechanism of action.

Honey

Honey has a long history of use in topical wound management [6]. There is only a small case series of its use as a topical agent for deep PJI wounds at the time of reimplantation [7]. In this series, sterile, industrially-manufactured SurgiHoney (SurgiHoney RO, Southmoor, Abingdon, United Kingdom) was used in salvage cases. No adverse effects were reported, but no conclusions regarding efficacy can be drawn.

Hydrogen Peroxide

Dental publications are a resource that orthopaedic surgeons should review for parallel implant experience. One such paper is by Gustumhaugen et al. [8], who found that hydrogen peroxide (H_2O_2) was an effective biofilm debriding agent, especially in combination with mechanical debridement.

Local Anesthetic

Indirect evidence comes from an experimental study of peritonitis in a rat model. Lavage with normal saline and bupivicaine prolonged survival [9]. Studies on ropivacaine have also proved encouraging [10].

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1.16. PREVENTION: OPERATING ROOM, SURGICAL TECHNIQUE

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QUESTION 1: Should the knife blade be changed after skin incision for deep dissection?

RECOMMENDATION: Yes. The scalpel should be changed after making the skin incision. There are studies demonstrating that bacteria from the superficial planes of the skin can contaminate the scalpel and potentially transfer this into deeper tissues.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 6%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Since infections can have such a devastating effects on total joint arthroplasty, it will always be necessary to search for methods to reduce contamination. The main sources of contamination come from skin and particles in the air of the operating room [1,2]. Controversy remains about the use of separate blades for skin incision and internal use, although this practice has been discredited [3–10].

Preoperative preparation of skin with antiseptics can help reduce the number of microorganisms, but cannot completely eradicate them, especially resident flora. Hypothetically, whenever the skin is incised microorganisms that colonize the deeper layers of skin can contaminate the exposed tissues and lead to surgical site infections (SSIs) [11–13].

A systematic review was conducted on this subject following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and the PRISMA statement. A comprehensive search of the literature was carried out in February 2017 using electronic databases PubMed, Medline and the Cochrane Library. The search terms used were "Arthroplasty AND Infection AND Knife OR Blade." Only English studies were reviewed. This yielded four results after duplicates were removed. Because of the low numbers of studies done on this subject, there was no limitation on the type of the articles that were reviewed. Cross references revealed four more results. One study was not analyzed as it was not comparative, leaving seven reports for analysis.

The contamination rates of skin and deep knives were assessed with the Fisher's exact test. Seven studies were included in the final analysis (Table 1). None of the studies showed a direct relationship between knife contamination and SSIs. Six studies could not demonstrate a difference in the contamination rates between the skin and deep knives [5,8–12]. In one study, the deep knife was significantly more contaminated then the skin knife [7]. Analysis of all seven studies together shows higher contamination rate for deep knives than skin knives, mostly due to the latter study.

One recent study by Schindler et al. performed on patients having hip or knee arthroplasty compared the contamination rated of skin blades, inner blades and controls [12]. Even though there were

TABLE 1. Summary of included literature pertaining to knife blade contamination and deep infection

Author	Year	Total			Contaminated			Same Organism at Skin and Deep Knife	Deep Infection	P Value
		Skin knife	Deep knife	Control knife	Skin knife	Deep knife	Control knife			
Fairclough [5]	1983	187	187	-	8	8		2	1*	1
Hill [8]	1985	93	93		8	8		2	0	1
Grabe [7]	1985	358	358		29	67		11	7**	0.0003
Ramón [9]	1994	115	115		6	13		2	2	0.15
Schindler [12]	2006	203	203	203	31	22	13	3	-	0.18
Ottesen [10]	2014	277	277	277	8	5	5	1	0	0.58
Trikha [11]	2016	92	92	92	6	7	0	2	5**	1
Total		**1,325**	**1,325**	**572**	**96**	**130**	**18**	**23**	**15**	**0.03**

*Identified pathogen of wound infection was not identified at either skin or deep knives

**Superficial infection

no differences between the groups with regards to contamination rates they found higher incidences of skin pathogens isolated in the skin knife than the deep or control knives, leading to the assumption that these specimens were not contaminated in the laboratory. The development of deep or superficial infection was not evaluated in this study. Given the scarce literature, even with advanced research technologies, and the difficulty with which researchers are able to define the question, a low level of strength is provided.

Taking into account the low costs of changing blades, the methodology of all the studies discussed above and the potentially devastating consequences of prosthetic joint infection, we find it hard to recommend against changing the knife after skin incision is made. Therefore, we advocate maintaining the old surgical technique of changing the skin scalpel to continue to deeper planes with a new blade.

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QUESTION 2: Does operative time affect the risks of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: Yes. There is an association between prolonged operative times and SSIs. Prolonged operative times may be a result of a considerable and inescapable level of complexity of the surgery. Coordinated efforts to reduce the operative times without technically compromising the procedure can provide additional benefits for infection prevention.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 99%, Disagree: 0%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Several systematic reviews and meta-analyses have demonstrated an association between operative times and SSIs as well as PJIs. Urquhart et al. [1] published a systematic review on risk factors for SSIs after primary total hip arthroplasty (THA), and found longer durations of surgery to be an independent risk factor for deep SSIs based on two studies [2,3], one of which was not specific to joint arthroplasty surgery. Kong et al. published a meta-analysis and found operative times to be associated with SSIs following primary THAs or total knee arthroplasties (TKAs) (standardized mean difference: 0.49, 95% confidence interval (CI) 0.19 to 0.78) [4]. Cheng et al. performed a meta-analysis over a variety of surgical procedures including orthopaedic surgery [5]. Pooled analysis demonstrated that the associations between extended operative times and SSIs typically remained statistically significant, with close to twice the likelihood of SSIs observed across various time thresholds [5]. The likelihood of SSIs increased with increasing time increments. For example, a 13%, 17% and 37% increased likelihood for every 15, 30 and 60 minutes of surgery, respectively [5]. On average, across various procedures, the mean operative time was approximately 30 minutes longer in patients with SSI compared to those patients without [5].

Administrative and registry databases have also linked increased operative times to SSIs/PJIs with statistical significances. Investigating 99,444 patients using the National Surgical Quality Improvement Program (NSQIP) database between 2011 and 2013, Duchman et al. found SSI was increased for primary total joint arthroplasty (TJA) procedures lasting > 120 minutes [6]. In their multivariate analysis, operative times exceeding 120 minutes remained an independent predictor for any complication and for wound complication, with each 30-minute increase in operative times beyond 120 minutes further increasing risks [6]. In an analysis of 56,216 primary TKAs from a registry collecting data from 45 locations in 6 US geographical regions, Namba et al. identified a 9% (95% CI 4 to 13%) increase in the risk of deep SSI per 15-minute incremental increase in operative time [7]. Decreased operative times were also associated with a lower risks of infections [7]. A study of 66,650 primary total hip arthroplasties reported to the Norwegian Arthroplasty Register during 1987 to 2001, revealed that cemented implants with operating time over 150 minutes were associated with an increased risk of revision due to infection [8]. Kurtz et al. investigated 69,663 patients over the age of 65 years undergoing TKAs from a Medicare claims database between 1997 and 2006, and found that longer duration procedures were at greater risk of PJI (adjusted hazard ratio for > 210 minutes vs. < 120 minutes = 1.59) [9]. In a multivariate analysis of 6,848 cases from 26 hospitals participating in the Korean Nosocomial Infections Surveillance System, Song et al. found that prolonged duration of surgery (above the 75th percentile) was an independent risk factor for SSIs

in THA, but not for TKA [10]. Dicks et al. found patients undergoing TKAs or THAs that had an operative duration > 75th percentile had a higher risk of SSI [11]. Additionally, Peersman et al. found that an operating time of more than 2.5 hours for TKA was associated with an increased incidence of infection and that operating time can predict those patients at risk [12].

There are inherent limitations to database studies, such as significant heterogeneity of the samples, differences in data collection, and varying definitions of PJIs within the sample. Single institutional work is therefore useful in this context because patients are subjected to the same care protocols, and more reliable data collection may be obtained. However, high-quality institutional studies have been limited by a lack of adequate sample size, absence of multivariate analysis and varying definitions of PJI. Peersman et al. compared a cohort of 113 PJIs following TKA with a control cohort of non-infected primary TKA matched for gender and age [13]. The mean duration of surgery for PJI vs. non-infected cases (127 vs. 93 minutes) was found to be a statistically significant risk factor for infections. Limitations of this study were that the control group was only matched for age and gender, but not for other important confounding factors. Additionally, the infection group included both index primary and revision cases, while the control group only included primary cases. In another single institutional study of 5,277 TJA, overall infection rate was 0.98% (51/5,277) [14]. Using a binomial generalized linear model, prolonged operative time was found to be associated with an increased incidence of infection ($z = 4.325$, $p < 0.001$). In TKA, a longer tourniquet time ($z = 2.867$, $p = 0.004$) was predictive of SSIs as well [14]. Again, the major limitation of this study was that it did not include confounding factors such as diabetes mellitus, rheumatoid arthritis or obesity. In a retrospective review by Wang et al. [15], 17,342 unilateral primary TKA and THA performed by 7 high volume surgeons, patients with an operative time of > 90 minutes were found to have higher incidence of SSIs and PJIs (2.1 and 1.4%,) compared to cases lasting 60 to 90 minutes (1.1 and 0.7%), and those lasting ≤ 60 minutes (0.9 and 0.7%). This trend was statistically significant ($p < 0.01$). After controlling for multiple confounding factors with multivariate regression, prolonged operative times remained an independent risk factor for 90-day SSI (odds ratio (OR): 1.01, 95% CI 1.002 to 1.016, $p = 0.009$) and PJI within 1 year (OR: 1.01, 95% CI 1.00 to1.02, $p = 0.040$) [15].

In contrast, some studies have failed to demonstrate such a correlation, especially when aiming to control for confounding variables. In a retrospective review of 9,245 TJA patients (4,185 TKAs and 5,060 THAs), longer operative times were a predisposing factor for PJI with univariate analysis, but multivariate analysis that adjusted for confounding factors revealed that operative time was not an independent predisposing factor for PJI [16]. Similarly, Naranje et al. found that after controlling for age and sex, there was no significant evidence that increased operative time increased the hazard of revision resulting from infection [17]. However, they did show a 15-minute increase in operative time increased the hazard of revision for infection by 15.6% on average ($p = 0.053$; 95% CI 0.0% to 34.1%) [17]. Saleh et al. retrospectively reviewed 1,181 TKA and 1,124 THA primary procedures. Of the factors examined, only hematoma formation and days of postoperative drainage were significant predictors of SSI or deep wound infection, and operative time was not a significant risk factor [18]. Carroll et al. conducted a retrospective cohort study of 964 patients undergoing THA and TKA in one institute over 18 months.

Although tourniquet times were found to be an independent risk factor for superficial wound complication (defined by either a superficial incisional SSI or prolonged wound ooze within 30 days of surgery) in the TKA cohort, operative times were not an independent risk factor in their analysis [19]. Lastly, Kremers et al. found no significant relationship between SSIs and operative times (per 10-minute intervals) [20].

There is considerable evidence that suggests an association between prolonged operative times and SSIs/PJIs with a few studies suggesting no correlation. Steps to minimize intraoperative delay should be taken, and care should be exercised when introducing measures which prolong the duration of joint arthroplasty surgery.

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QUESTION 3: Do antibiotic coatings on implants reduce the rates of surgical site infections/ periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: The use of antibacterial coatings on implants has been shown to reduce SSIs and/or PJIs based on in vitro and pre-clinical animal model studies. The use of antibiotic-coated implants in small series of patients appears to be encouraging. Larger-scale studies to prove the value of these technologies are needed.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 6%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Implanted biomaterials continue to play a key role in orthopaedic surgery. However, infections surrounding these implanted biomaterials remain a leading cause of failure, especially in total hip and knee arthroplasties [1–3]. The biofilm theory and its role in the propagation of bacterial growth is postulated to play a quintessential role in the etiology and pathogenesis of PJIs in modern-day total joint arthroplasties (TJAs) [4–8]. Surface roughness, hydrophobicity and electrostatic charge are important characteristics of implanted biomaterials that are exploited by bacteria to promote adherence [9,10]. Strategies proposed to reduce the rates of these complications have included the use of implants coated with antiseptic materials or antibiotic agents. Antibacterial coatings engineered for the surfaces of implanted biomaterials have been an evolving technology over the last three decades [11]. Romano et al. described ideal characteristics of future antibacterial coatings, namely that they would be proven in vivo by demonstrating acceptable antibacterial properties towards a large spectrum of organisms, easy handling, cost-effectiveness and lack of local or systemic toxicity while ensuring bone healing, on-growth or in-growth [9].

Antibacterial coatings can be categorized into three groups: (1) perioperative antibacterial local carriers or coatings (LCC), (2) passive surface finishing/modification (PSM) and (3) active surface finishing/modification (ASM) [9].

The first group, LCC, are antibacterial carriers or coatings that are applied to implants at the time of surgery. The most popular and well-studied vectors in this category include antibiotic-laden bone cement, used when coating intramedullary nails or total joint components [12]. Antibiotic-laden hydrogel that may be applied to the implant by the surgeon has been shown to reduce surgical site infections in a multicenter randomized controlled trial of 380 patients undergoing primary and revision total hip and total knee arthroplasties [13]. Similarly, a pilot study of second-stage implantation for prosthetic joint infections utilized implants coated with a resorbable calcium based bone substitute mixed with gentamycin or vancomycin [14]. At a minimum follow-up of one year, 95% of patients did not show any clinical signs of infections. However, no control group was used in this pilot study [14]. Furthermore, these studies, as well as other smaller cohorts that have been reported, are underpowered to make definitive recommendations for its widespread use.

The second group, PSM, revolves around the premise that chemical and/or physical modifications to the surface of an implanted biomaterial may reduce bacterial capabilities of adherence, and thus, prevent biofilm formations. These modifications are made without the planned release of bacteriostatic or bacteriocidal agents into the surrounding tissues. Such technology includes treatment of the surface layer of an implant with ultraviolet (UV) light irradiation to increase the hydrophilicity of the implant, which decreases bacterial adherence [15]. Changing the morphology of the surface layer of implants without decreasing the reliability of osseointegration has been proven capable of decreasing bacterial adherences in in vitro studies [16–19]. Polymer coatings (hydrophilic polymethacrylic acid or polyethylene oxide) or hydrogel coatings can also be applied to titanium implants, which helps deter bacterial adhesions [18,20–24]. PSM has great potential for future use on implanted biomaterials, however, there is concern regarding the osseointegration with coatings or surface modifications with strong anti-adhesive capabilities. Future in vitro and in vivo studies are needed prior to widespread clinical application.

The third group, ASM, includes modifications to the surface of the implant that impart pharmacologically-active antibacterial agents such as antibiotics, antiseptics, metal ions and/or organic compounds [9]. Antibacterial surface innovation largely revolves around metal ions such as magnesium, gold or silver [25–31], as well as non-metal elements such as chlorohexidine [32]. Antibiotics may be sprayed on or covalently bonded to the implant surface [33], applied via hydrogel or coating [13,34] or contained in and released via nanotubes [35,36]. While there is a myriad of vectors to deliver antibiotics to the surrounding tissue, there is a paucity of conclusive in vitro studies, and a relative lack of in vivo studies demonstrating safety and efficacy with this technology. Further confounding ASM is the wide variability of coatings studied. This makes it tremendously difficult to draw conclusions from the current literature regarding ASM. While studies have shown that antibiotic coatings do not affect bone healing in animal models [37,38], this technology has not been studied clinically.

Perhaps the most well-studied antibacterial coating are antiseptics, such as metal ions impregnated into the implant or applied via coating. Both in vitro and in vivo animal models have demonstrated significant antibacterial effects [23,25,26,28,31,36,39–41]. Additionally, clinical studies of silver-coated endoprostheses have demonstrated the efficacious antiseptic effects of the metal-ion coating in reducing infection [42–44]. However, these studies are largely retrospective in nature, and underpowered to render conclusive evidence supporting the widespread application of such technologies. While there are concerns of metal-ion toxicity that may result from such coatings, several studies have demonstrated little to no evidence of toxicity or side-effects [30,40,45]. Metal-ion coatings appear to the most promising in terms of efficacy and near-future implementation based on review of the present literature surrounding antibacterial coatings.

Despite the promise of these individual reports, the paucity of high-level controlled trials in the setting of arthroplasty, suggests that it is too early to conclude that antibiotic coatings will reduce the

rates of SSIs/PJIs following primary or revision procedures. However, these strategies could prove to be beneficial in high-risk primary or revision cases. Further high-quality studies are needed to address these questions.

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QUESTION 4: Does the size of an implant (volume) used during orthopaedic procedures influence the incidence of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: While a smaller implant may theoretically represent a smaller substrate for colonizing bacteria, there have been no conclusive studies linking implant size and the incidence of subsequent PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 85%, Disagree: 10%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

An OVID Medline search failed to identify any literature investigating relationships between component sizes and incidences of PJIs. There are several retrospective studies reporting lower incidences of PJIs in patients undergoing unicompartmental knee arthroplasties (UKAs), than those undergoing total knee arthroplasties (TKAs) [1–3]. Furnes et al. reviewed the Norwegian Arthroplasty Register and found an overall incidence of PJIs following UKAs to be much less than that for TKAs (0.2 vs. 1.2%, relative risk: 2.8, p = 0.01) [3]. This finding may be attributed to the smaller implant burden of a UKA and thus a smaller substrate for colonizing bacteria however, there are many other potential explanations. Numerous factors are associated with an incidence of PJIs following arthroplasty, including host-related factors (e.g., gender and obesity) [4–9] and surgical factors. Sershon et al. also identified demographic variables in predicting component sizes in TKAs [10]. While increased weight and male gender were found to be associated with larger implants, there are other reasons for the causal association with PJIs that goes beyond the potential of implant size playing a role.

Even if a causal relationship between implant size and the incidence of PJIs were to be found, one needs to remember that larger implants are often used during more complex procedures such as revision or oncologic reconstructions. The nature of these procedures, in terms of increased operative times, higher blood losses and worse health status of the host, would play more critical roles in causing PJIs than the mere sizes of the implants. In addition, larger implants are used in cases with bone losses and the corresponding decreased soft tissue attachments to the bones, leading to higher areas of dead spaces and subsequent seroma or hematoma formations, eventually lending to wound related issues.

There is currently no data that evaluates the relationship between the size of an implant used during orthopaedic surgery and the risks for subsequent SSIs/PJIs. Further studies are needed to establish any relationship between component size and the incidence of PJIs. These studies would be difficult to perform, as it would be difficult to isolate implant size as an independent variable.

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QUESTION 5: Does the use of C-arm intraoperatively increase the risk for subsequent surgical site infection/periprosthetic joint infection (SSI/PJI) in patients undergoing orthopaedic procedures?

RECOMMENDATION: There are no studies that link the use of intraoperative C-arm with a higher rate of subsequent SSI or PJI in orthopaedic surgery. However, based on available studies, it appears that the "sterile" cover of C-arm is often contaminated during the surgery. We recommend that all efforts be made to prevent the cover (or any other part) of the C-arm from coming into contact with the operative field.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 97%, Disagree: 1%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive search of the literature was performed on PubMed and Google Scholar using the terms: C-arm, fluoroscopy, image intensifier with contamination, SSI, PJI and infection. A total of 96 articles potentially relevant to the subject were identified. The articles were reviewed and the majority were excluded due to being non-medical or technique papers. Of the studies that were reviewed, none used SSI/PJI as an outcome.

One study retrospectively reviewed 75 total hip arthroplasty (THA) procedures during which intraoperative fluoroscopy was utilized versus 72 THA procedures in which no fluoroscopy was utilized. There was no difference in the incidence of infection between the two cohorts [1]. It is acknowledged that the cohort size in the study was extremely small (possibly too small to be able to examine the potential risk for subsequent SSI/PJI added with the use of intraoperative C-arm). To our knowledge, no other study examining the potential link between the use of C-arm and subsequent SSI/PJI exists. We realize that such studies would be difficult to perform, as C-arm could be an essential part of an orthopaedic procedure and randomizing patients is only possible when the C-arm is not considered essential.

There have been studies performed to evaluate contamination of the C-arm during surgery. One study was performed during 30 consecutive cases undergoing fracture fixation. Cultures were obtained after initial draping and every subsequent 20 minutes. Interestingly, on initial draping 17% of covers were contaminated. By 80 minutes, 80% of covers were contaminated. Only five cases were not contaminated during the surgery [2]. The findings of the study are of concern in that a C-arm appears to be a potential source of contamination of operative field contamination. Surgeons should not assume that the "sterile" cover applied to the C-arm actually remains sterile.

There is an absence of any concrete evidence linking the use of an intraoperative C-arm to an incrase in the incidence of subsequent SSI/PJI. There is, however, evidence that a C-arm can be a source of potential contamination of the operative field. The use of a C-arm should be limited to procedures that truly require intraoperative imaging. During these cases extreme caution should be applied to prevent contact between the cover, or any part, of a C-arm and the operative field. The C-arm and its cover should be considered contaminated from the start of the procedure.

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QUESTION 6: Does the use of recently-introduced technologies (navigation, robots, etc.) influence the incidence of surgical site infection/periprosthetic joint infection (SSI/PJI) after orthopaedic procedures?

RECOMMENDATION: The use of computer-navigation, patient-specific instrumentation and robot-assisted surgery during total joint arthroplasty has not been shown to increase the risk of subsequent SSI/PJI. However, an increase in operative time that may occur as a result of use of these technologies may increase the risk of subsequent SSI/PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 84%, Disagree: 9%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

There has been an influx of new technology in the realm of total joint arthroplasty (TJA) over the past two decades with the aim of improving outcomes. New technologies include computer-assisted arthroplasty, robotic-assisted arthroplasty and patient-specific instrumentation (PSI). Some of these technologies are gaining acceptance in the field of hip and knee arthroplasty. There is, however, a paucity of literature regarding the use of these technologies in other orthopaedic procedures and the link between the use of these technologies and the potential for an increase the rate of subsequent of SSI/PJI.

Computer-assisted surgical (CAS) navigation was introduced in the 1990s and has steadily gained traction in recent years. There are three distinct types of CAS arthroplasty including imageless, preoperative image-based and intraoperative image-based systems. Imageless systems feature accelerometer-based or optical navigation systems, whereas image-based CAS use radiological imaging to form 3D models of the patient's specific anatomy [1,2]. The main aim of CAS in arthroplasty is to improve component position and restore the mechanical axis [3,4].

While there are many studies examining the radiological and functional outcomes of CAS, only a limited number examine rates of SSI/PJI in computer-navigated arthroplasty. Regardless, both retrospective and prospective studies report similar rates of infection between CAS and conventional arthroplasty, with patient follow-up ranging from 12 weeks to 10 years [5–17]. Meta-analyses comparing the outcomes of navigated versus conventional knee arthroplasty performed by Bauwens et al. and Moskal et al. also revealed similar rates of postoperative infection for the two patient groups [18–19]. The longer operative time associated with full computer-navigated surgery are a potential risk factor for PJI, but does not appear to affect the rates of PJI in the current literature [7–21].

In most types of navigation-assisted surgery, several temporary pins must be placed (an exception being small handheld navigation devices), either within the operative field or percutaneously through

separate stab incisions, hence introducing the possibility of contamination of the operative field and pin-site infections. However, studies by Kamara et al. and Owens et al. revealed low incidence of pin-site infections (0.36% and 1.2%, respectively), concluding that the complication rates due to temporary pin insertion is low [22,23].

Robotic systems were developed to improve the accuracy of implant selection, placement, alignment and bone resection during arthroplasty [1,24,25]. There have been no reports of increased rates of prosthetic joint infection after robot-assisted arthroplasty. Song et al. performed simultaneous bilateral total knee arthroplasty (TKA) on 30 female patients (1 knee replaced by robotic-assisted implantation and the other by conventional implantation) in a prospective randomized study and found no major adverse events related to the use of the robotic system (such as deep infection or loosening requiring revision) [26]. It is recognized that the cohort size in the latter study was excessively small to examine the issue of infection. Hill et al. proposed higher infection rates as a possible limitation to the use of robotic systems in arthroplasty due to the use of an autonomous system, yet there is limited data to support this assertion at this time [27].

PSI was recently introduced with the aim of improving component alignment and potentially reducing the risk of subsequent revision. For this, MRI, CT and/or plain radiographs are utilized by manufacturers to develop three-dimensional models of the patient's anatomy prior to surgery. From these, disposable cutting blocks are fabricated which are specific to each patient. In theory, PSI can reduce operative time as well as the number of surgical instrument trays required to perform TKA, which may in theory reduce the risk of PJI [28–30]. The literature is, however, sparse regarding infection rates post-arthroplasty for patients who have undergone TKA using PSI. Schoenmakers et al. followed 200 consecutive patients who had undergone PSI-aided arthroplasty by a single surgeon for 5 years and reported rates of prosthetic joint infection similar to those found in conventional arthroplasty [31]. Alvand et al. performed a prospective randomized controlled study comparing PSI versus conventional unicompartmental knee arthroplasty, and found similar rates of superficial infection between the two groups [32].

At present, there is no definitive literature to suggest that the rates of SSI/PJI are increased or decreased when TJA is performed using the recently introduced technologies such as robotics, navigation or patient-specific implants. Most studies examining these new technologies are not adequately-powered to examine the rates of SSI/PJI. Larger-scale studies are needed to evaluate this issue.

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1.17. PREVENTION: BLOOD CONSERVATION

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QUESTION 1: Does allogeneic blood transfusion increase the risk of surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Yes. Allogenic blood transfusion is associated with an increased risk of SSI/PJI.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 94%, Disagree: 3%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Allogeneic blood transfusion is a standard treatment to correct anemia in the setting of perioperative blood loss [1,2]. Data derived predominantly from retrospective studies have suggested that the administration of allogeneic blood transfusions may increase the risk of surgical site infection in arthroplasty and other surgical fields [1]. Postulated mechanisms for this occurrence include transfusion-associated immunomodulation (TRIM), in which infusion of circulating antigens present in the transfused blood product lead to a down-regulation of the host immune response [3]. Alternatively, this association may represent confounding factors such as hematoma formation, the presence of comorbid conditions or more prolonged, complex surgeries [4,5].

The association between allogenic transfusion and SSI and PJI has been explored in two recent meta-analyses. The meta-analysis conducted by Berríos-Torres et al. [4] for the Centers for Disease Control and Prevention (CDC) guidelines for the prevention of surgical site infection examined the association between blood transfusions, including both allogeneic and autologous transfusions. When comparing allogeneic transfusion to no transfusion, they identified 4 observational studies (n = 5,737) that showed that allogeneic blood was associated with increased odds of infection compared with no transfusion (odds ratio (OR): 1.96, 95% confidence interval (CI) 1.46 to 2.63, $p < 0.01$, $I^2 = 0$) [2,4,6–8]. The second analysis compared allogeneic to autologous blood transfusions. This analysis also showed that allogeneic blood transfusions was associated with increased odds of infection when compared to autologous blood transfusion (OR: 4.53, 95% CI 2.37 to 8.65, $p > 0.01$, $I^2 = 0$) [6,8,9]. They concluded that there were uncertain tradeoffs between the benefits and harms of transfusion. However, the authors noted that there was no evidence to support withholding transfusion as a strategy to prevent surgical site infection in patients with anemia meeting transfusion criteria.

A second meta-analysis was published by Kim et al. [10]. This meta-analysis identified six studies (n = 21, 770) [5,6,8,11–13]. When patients who received allogeneic transfusion were compared to a combined group of patients who either received autologous or no transfusion, the patient cohort who received allogeneic transfusion was associated with increased odds of SSI (OR: 1.71, 95% CI 1.23 to 2.40; $p = 0.002$, $I^2 = 0.506$). The second component of the meta-analysis compared patients who received allogeneic transfusion to patients who received no transfusion. Patients who received allogeneic transfusions remained at increased odds of infection when compared to patients who received no transfusions (OR: 1.55, 1.11 to 2.17, $p = 0.01$, $I^2 = 0.110$). Therefore, the authors concluded that strategies that reduce the need for allogeneic transfusion should be considered in order to prevent SSI/PJI [10].

A review of the literature in electronic databases was performed (Table 1). In addition to the 2 meta-analyses, 20 studies met the inclusion criteria. Studies were published over a 20-year period (1997 to 2017). One study was a small (n = 100) randomized controlled trial and the remainder of the studies were observational studies. Most studies included lower extremity arthroplasty except two that included shoulder arthroplasty. A range of definitions for surgical site infection were applied. Data was analyzed using a random effects model to account for between-study heterogeneity.

Allogeneic Transfusion Versus No Transfusion

Fifteen observational studies were included in the meta-analysis comparing allogeneic transfusion to no transfusion [2,5–8,11–21]. One study by Llewelyn et al. [7] evaluated patients before and after transfusions with leukoreduced and non-leukoreduced allogeneic transfusions. These time periods were analyzed separately. The results show that patients who received allogeneic transfusions were associated with increased odds of surgical site infections when compared with patients who received no transfusions (pooled OR: 2.06, 95% CI 1.56 to 2.72, $p < 0.001$, $I^2 = 0.669$, Fig. 1).

Allogeneic Transfusion Versus Autologous Transfusion

Five observational studies were included in the meta-analysis comparing allogeneic transfusion to autologous transfusion [6,12,13,17,22]. Patients who received allogeneic transfusions were associated with an increased risk of surgical site infection when compared with patients who received autologous transfusions (pooled OR: 2.46, 95% CI 1.57 to 3.84, $p < 0.001$, $I^2 = 0.431$, Fig. 2).

Conclusion

Allogeneic blood transfusion is associated with an increased risk of SSI when compared to no transfusion or autologous transfusion. The data contained in the meta-analysis was derived from observational studies with significant heterogeneity. The underlying pathophysiological mechanism for this association has not been well-defined. In keeping with the conclusions drawn by Berríos-Torres et al. in the CDC guidelines, there is no data to support the withholding of allogeneic transfusion in patients with symptomatic anemia as a strategy to prevent SSIs [4]. Furthermore, the data presented supports that allogenic blood transfusion does increase the risk of SSI/PJI.

TABLE 1. Characteristics of included studies

Author	Year	Ref	Design	Population	Comparison	Allogeneic		No Transfusion		Autologous	
						SSI	No SSI	SSI	No SSI	SSI	No SSI
Shenolikar	1997	14	RCT	TKA	AL/AU	1	39	.	.	0	42
Levi	1998	15	OB	THA	AL/NIL	11	145	20	519	.	.
Borghi	2000	16	OB	THA + TKA	AL/AU	4	274	.	.	13	2,593
Rosencher	2003	6	OB	THA + TKA	AL/AU/NIL	36	963	22	1,158	11	1,300
Llewelyn	2004	7	OB	THA + TKA	NoLR AL/NIL	43	563	31	840	.	.
Llewelyn	2004	7	OB	THA + TKA	LR AL/NIL	32	605	22	777	.	.
Innerhofer	2005	8	OB	THA + TKA	AL/AU/NIL	3	97	1	100	0	85
Weber	2005	2	OB	THA	AL/NIL	1	91	1	351	.	.
del Trujillo	2008	9	OB	THA	AL/AU/NIL	2	30	0	25	0	51
Dowsey	2008	11	OB	THA	AL/NIL	11	418	11	764	.	.
Dowsey	2009	17	OB	TKA	AL/NIL	8	292	10	904	.	.
Pedersen	2009	18	OB	THA	AL/NIL	5	2,249	5	2,249	.	.
Basora	2010	5	OB	TKA	AL/NIL	22	313	39	536	.	.
Drosos	2012	19	OB	TKA	AL/AU/NIL	13	58	6	79	8	84
Friedman	2014	12	OB	THA + TKA	AL/AU/NIL	108	3,854	123	6,190	33	1,869
Frisch	2014	20	OB	THA + TKA	AL/NIL	6	248	6	1,304	.	.
Newman	2014	13	OB	THA + TKA	AL/AU/NIL	14	822	12	1,594	6	904
Smucny	2015	21	OB	TSA	AL/NIL	110	31,577	310	332,607	.	.
Tornero	2016	22	OB	THA	AL/NIL	7	164	3	106	.	.
Everhart	2017	23	OB	TSA	AL/NIL	6	85	16	600	.	.

RCT, randomised controlled trial; OB, observational study; THA, hip arthroplasty; TKA, knee arthroplasty; TSA, shoulder arthroplasty; AL, allogeneic transfusion; AU, autologous transfusion; NIL, no transfusion; LR AL, leucoreduced allogeneic transfusion; NoLR AL, non-leucoreduced allogeneic transfusion; SSI, surgical site infection.

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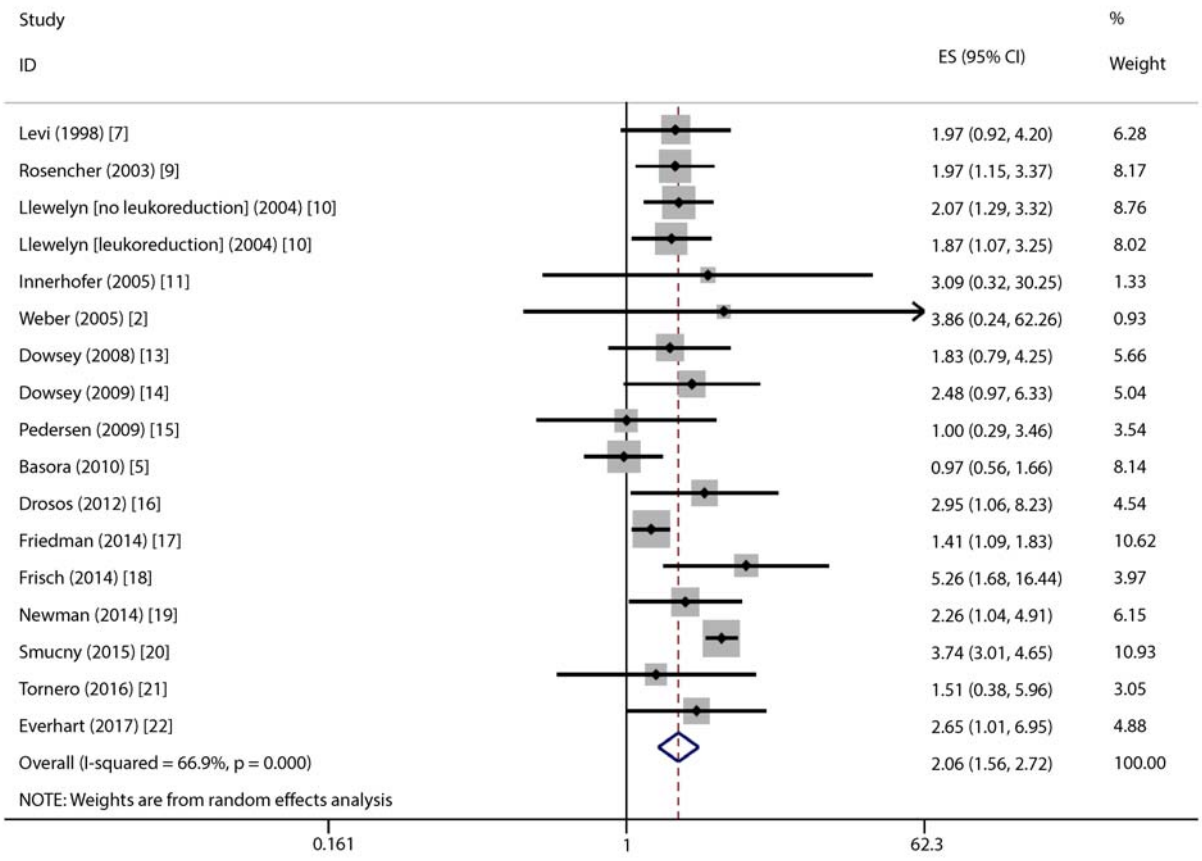

FIGURE 1. Forest plot comparing allogeneic transfusion to no transfusion. (CI, confidence interval; ES, effect size).

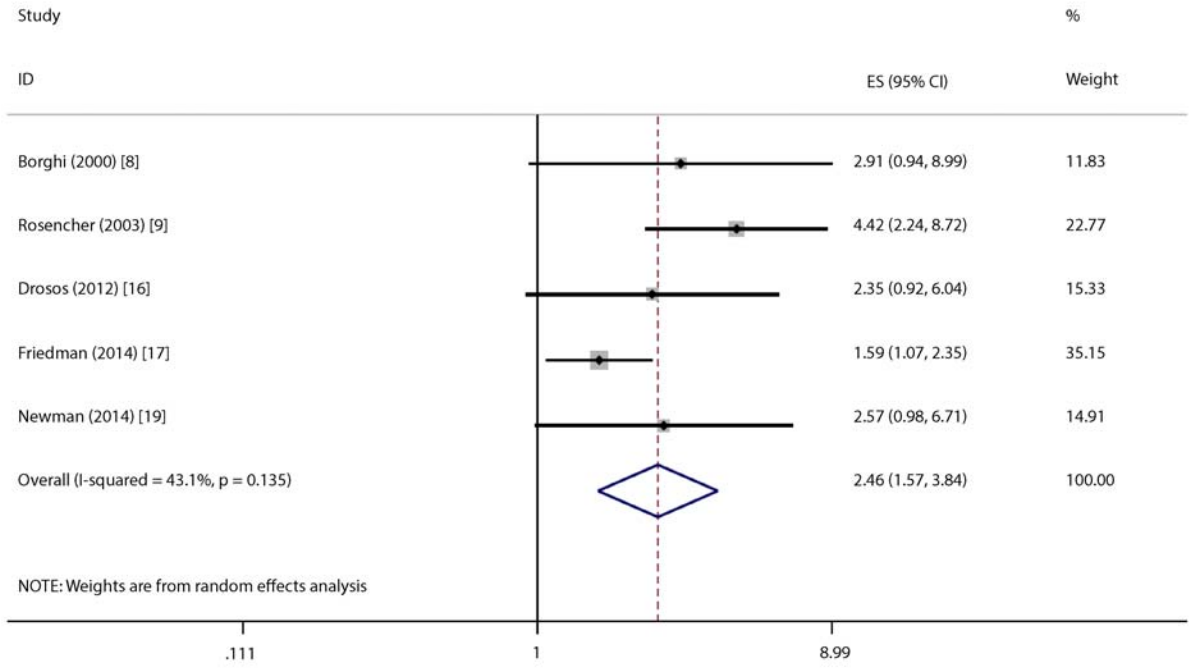

FIGURE 2. Forest plot comparing allogeneic transfusion to autologous transfusion. (CI, confidence interval; ES, effect size).

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QUESTION 2: Can intraoperative or postoperative blood salvage be utilized in patients undergoing reimplantation for treatment of periprosthetic joint infectcion (PJI)?

RECOMMENDATION: Unknown. The limited published data on this subject suggests that the use of intraoperative or postoperative blood salvage in patients undergoing reimplantation for treatment of PJI may be beneficial, but also poses a potential risk of bacterial dissemination. Further studies are needed to evaluate the risks and benefits of this strategy.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 92%, Disagree: 4%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Different strategies have been used to avoid allogeneic red blood cell transfusion (ARBCT) in total joint arthroplasty due to its deleterious effects, including transfusion-associated lung injury, circulation overload and, most importantly, increased risk of PJI [1,2]. Cell salvage offers a safe, resource-saving and relatively inexpensive method to avoid ARBCT [1]. However, the main concern remains in its use in the setting of reimplantation given the possibility of persistent, undetectable infection.

There is limited data available in literature specific to the use of intraoperative or postoperative blood salvage to be utilized in patients undergoing reimplantation for the treatment of PJI. A systematic review was performed specifically evaluating if it is safe to re-infuse these products in this setting. Several level III and IV studies have examined the incidence of bacterial contamination of blood salvage equipment in elective non-orthopaedic surgery and have demonstrated little if any evidence of bacterial dissemination from blood salvage devices [3–6].

The use of intraoperative cell salvage has been supported in aseptic revision and primary hip and knee arthroplasty. It has been seen as efficacious in reducing the need for ARBCT and demonstrated cost-effectiveness [7]. A systematic review by Carless et al. evaluated 75 studies that investigated the effectiveness of cell salvage in different surgical specialties including orthopaedics [8]. They concluded that there is sufficient evidence to support the use of cell salvage. Furthermore, with advances in washing and filtration technology, new cell salvage devices continuously improve and provide a high-quality blood product for re-infusion [9].

Few absolute contraindications have been clearly stated for blood salvage [10]. Anything that results in lysis of the red blood cells is defined as an absolute contraindication. Blood that has been mixed with fluids such as sterile water, hydrogen peroxide, alcohol or any hypotonic solution will result in red cell destruction. The reason for this contraindication is end-organ damage as a result of administering lysed red blood cells [11,12]. In terms of blood contamination or infection, it has been thought that administration of this contaminated blood will lead to bacteremia or sepsis and has been established as a relative contraindication. Studies have found that contamination of processed and re-administered units obtained intraoperatively range from 9 to 30% without clinical implications [3,13].

No evidence has been found in favor or against the use of blood salvage in the setting of reimplantation beyond the fact that it reduces ARBCT. Other specialties have shown it to be a safe procedure in contaminated scenarios. ARBCT increases the risk of PJI, and thus a careful evaluation should be performed before deciding to use intraoperative or postoperative blood salvage in these patients.

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QUESTION 3: Do antiplatelet drugs need to be withheld preoperatively to reduce the risk for subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Aspirin should not be withheld preoperatively. There is no evidence that withholding aspirin affects SSI/PJI rates and the cardiac and stroke risk associated with discontinuing aspirin outweighs any unproven, theoretical benefit with respect to SSI/PJI.

Clopidogrel should be withheld a minimum of five days preoperatively to reduce the risk for subsequent SSI/PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 6%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Antiplatelet drugs are commonly prescribed to reduce the risk of major vascular complications [1]. These medications interfere with one or more steps in platelet release and aggregation [2], causing a measurable decrease in the risk of thrombosis which cannot be dissociated from an increased risk of bleeding [3]. Because of the potential increased risk of bleeding, as well as concern for possible increased risk of SSI/PJI, the question whether to discontinue such medications perioperatively is an important topic in surgical care.

Irreversible Cyclooxygenase Inhibitors (i.e., Aspirin)

Aspirin, an antiplatelet agent widely used for its cardioprotective features, is taken by many total joint arthroplasty (TJA) patients preoperatively. It is an irreversible inhibitor of cyclooxygenase (COX), thus preventing the formation of thromboxane A2 (TxA2), a substance used in platelet aggregation [4]. It is rapidly absorbed, reaching peak levels in approximately 2 hours and has a dose-dependent half-life between 2 and 15 hours. Aspirin reduces mortality in patients undergoing cardiac and vascular surgery [4–7] and several studies have shown that aspirin therapy should never be discontinued after a coronary or cerebrovascular event [4,8–11]. Withholding aspirin increases the incidence of myocardial infarction, mortality and drug-eluting stent thrombosis and is an independent predictor of major ischemic events and death [4,12–15].

Deveraux et al. investigated the effects of aspirin versus placebo in non-cardiac surgery, including orthopaedic procedures. In this randomized controlled trial, 10,010 patients were grouped according to their aspirin use [16]. Use of aspirin significantly increased the risk of major bleeding, compared to placebo. However, there were no significant differences in infection rates between the aspirin and placebo groups. In a prospective cohort study of 139 TJA patients, Cossetto et al. found no difference in superficial wound infection or PJI between patients who continued aspirin perioperatively versus those who did not take aspirin [17]. In a retrospective cohort study of 175 TJA patients, Meier et al. demonstrated no difference in PJI between patients who discontinued aspirin 10 days preoperatively versus those who continued aspirin in the perioperative period [18]. Additionally, these two TJA studies found no significant difference in rates of bleeding in those taking aspirin before hip or knee surgery compared to those not taking antiplatelet drugs [17,18].

There is no evidence that withholding aspirin affects SSI/PJI rates. Because the cardiac and stroke risk associated with discontinuing aspirin outweighs any unproven, theoretical benefit for SSI/PJI risk, aspirin should not be withheld preoperatively.

Adenosine Diphosphate (ADP) Receptor Inhibitors (i.e., Clopidogrel, Prasugrel)

Clopidogrel is a platelet inhibitor indicated for use in patients with acute coronary syndrome, stroke or peripheral arterial disease. It is a thienopyridine antithrombotic agent, which prevents adenosine diphosphate (ADP)-mediated platelet aggregation, leading to the inhibition of fibrinogen binding to glycoproteins GPIIb and GPIIIa on the platelet surface [4]. The half-life of clopidogrel is approximately eight hours [19], but the effects of clopidogrel can be seen for up to seven days after discontinuation because there can be individual variation in recovery of platelet function, which depends more on the amount of initial inhibition by the drug and previous duration of therapy than on the number of days since cessation of the medication [4,12,20–23].

Several retrospective studies have found greater bleeding and/or increased risk of bleeding events in those taking clopidogrel before TJA or hip fracture surgery [24–26]. Patients who continued clopidogrel in the preoperative period were also significantly more likely to receive a blood transfusion within 24 hours of surgery and during hospitalization [27]. In a retrospective cohort study of 116 patients, Nandi et al. found that patients who stopped clopidogrel 5 or more days before TJA had lower rates of bleeding events, as well as significantly lower rates of reoperation for infection and antibiotics prescribed for the surgical wound when compared to those who stopped clopidogrel for 1 to 4 days, or 0 days before surgery [25]. Postoperative events did not vary with timing of clopidogrel resumption after surgery. In a case series of seven TJA patients by Shubert et al.,

12.5% of patients developed a PJI and 25% of patients required antibiotics for the surgical wound when clopidogrel administration was uninterrupted in the perioperative period [26]. In a retrospective cohort study of 142 primary or revision TJA patients, Jacob et al. did not find a difference in rate of PJI between patients that discontinued clopidogrel more than seven days preoperatively versus those who discontinued clopidogrel less than 7 days preoperatively [27]. These findings do not refute those of earlier studies, as the selection of the seven-day time point may have limited the ability of this study to detect a difference between groups.

Because of the increased risk of SSI/PJI with continuation of clopidogrel, it should be withheld a minimum of five days preoperatively to reduce the risk for subsequent SSI/PJI. It appears that clopidogrel may be resumed as early as the day of surgery, although the evidence for when to restart is limited [25].

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QUESTION 4: Is there a role for the administration of erythropoietin, hemotinics or other agents for patients with orthopaedic infections?

RECOMMENDATION: Yes. Erythropoietin used preoperatively in infected revision arthroplasty results in higher preoperative hemoglobin levels and lower allogeneic transfusion rates without compromising eradication of infection.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 82%, Disagree: 9%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

The use of erythropoietin to reduce transfusion requirements in primary arthroplasty is widely known, although as transfusion rates have decreased, the cost-effectiveness of this treatment has been questioned [1]. Similarly, the effect of tranexamic acid in reducing

transfusion requirement has been firmly established in primary arthroplasty [2], however much less is known about the effects of these agents in the case of orthopaedic infection. Although a recent paper has suggested that transfusion alone is not a risk factor for infection, the incidence of infection seems associated with other factors predictive of transfusion such as complexity or preoperative anemia, with all cause revision exhibiting much higher transfusion rates than primary arthroplasty [3]. As concurrent infection precludes autogenic transfusion, allogenic transfusion becomes the most common method of treating postoperative anemic, which carries with it inherent risk.

Only two case control studies have been found studying the effect of erythropoietin in infected arthroplasty, one in revision hip and one in revision knee for infection [4,5]. Both studies use an Epoetin alpha 40,000 unit dose administered between first- and second-stage revision, with different administration regimes. In both cases, transfusion rate and pre-reimplantation hemoglobin were used as primary end-points and both studies showed significant improvements in both metrics, without any noticeable increase in complications. It is notable, however, that both studies are at least 15 years old with no obvious follow-up work, since.

Several studies in the early 2000s examined the effects of the ani-fibrinolytic Aprotinin in the reduction of bleeding in studies including orthopaedic surgery for infection [6–8]. However, despite its effectiveness and widespread use in cardiothoracic surgery, Aprotinin was withdrawn from the market in 2008 due to concerns over increased mortality and renal failure. In light of this, the effects of Aprotinin have not been reviewed.

The beneficial effect of tranexamic (TXA) acid has been extensively reviewed in arthroplasty, but little research exists for patients with orthopaedic infections [9]. Only one small retrospective review examined the effects of topical TXA on infected arthroplasty patients undergoing two-stage revision. Those treated with TXA had lower hemoglobin droops and lower transfusion rates, with no increase in complications than those treated without TXA. However, it is not possible to form definitive conclusions from only one small retrospective study.

Only two studies were found examining the effects of erythropoietin in orthopaedic infections. Both case-control series indicate reduced transfusion rates and improved hemoglobin before re-implantation in two-stage revision for infection [4,5]. It must be noted that both studies are historic, with debatable relevance of comparing practice in the early 1990s (the time of the control cohorts) with contemporary care. However, the compelling success of these studies suggests that further investigation is required.

We note that a somewhat similar question from the 2013 International Consensus Meeting (ICM) resulted in strong consensus towards treatment of anemia with iron with or without erythropoietin to reduce the risk of transfusion. However, for this question the evidence is different from the 2013 ICM question. The current available literature does not appear to strongly support the same conclusion, primarily because the previously-referenced studies did not focus on infected cases [10,11].

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QUESTION 5: Does the use of tranexamic acid (TXA) reduce blood loss and need for allogeneic blood transfusion during primary total joint arthroplasty (TJA)?

RECOMMENDATION: Yes. The administration of intravenous (IV), topical and/or oral TXA is an effective strategy for reducing blood loss and the need for allogeneic transfusion during primary TJA.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Blood loss in primary TJA, especially total hip arthroplasty (THA), can be significant and is often under-estimated due to hidden blood loss [1–3]. Postoperative blood transfusion rates due to blood loss is estimated to be about 11% for total knee arthroplasty (TKA) and 18% for THA [1]. Therefore, several methods have been utilized to help reduce the risk of blood loss and need for allogeneic transfusion.

After discovery of the antifibrinolytic properties of TXA in the early 1960s by Shosuke and Utako Okamoto, TXA has become widely

used in many medical specialties [4,5]. Benoni et al. were the first to publish on the blood conserving properties of TXA in orthopaedic surgery [6]. Ever since their original publication, a growing body of literature has been published on the use of intravenous, topical and oral TXA in primary hip and knee arthroplasty. The overwhelming results from these studies and subsequent meta-analyses have demonstrated that TXA is a safe and effective method for reducing blood loss and the need for allogeneic blood transfusion.

IV TXA has been the most popular and widely-studied formulation in total joint arthroplasty with a recent literature search identifying more than 40 randomized clinical trials comparing intravenous TXA and placebo in primary TJA. Meta-analysis by Sukeik et al. and Yang et al. have proven the effectiveness of intravenous TXA compared to placebo in the setting of primary hip and knee arthroplasty [7,8].

Topical TXA is seen as an alternative to intravenous and oral routes of administration to provide local drug delivery. In two parallel-randomized control trials, Alshryda et al. investigated topical TXA in the setting of primary hip and knee arthroplasty by administering intra-articular 1 gm TXA or an equivalent volume of saline placebo [9,10]. Both studies provided evidence that topical TXA reduces the absolute risk for blood transfusion and reduces blood loss in primary hip and knee arthroplasties [9,10]. A systematic review and meta-analysis of 14 studies demonstrated similar results of a significant reduction in blood loss and need for transfusion when topical TXA was used compared to placebo, without an increase risk of complications [11]. When topical and intravenous TXA have been compared in a randomized clinical trial, Gomez-Barrena et al. found topical TXA in primary TKA demonstrated noninferiority to intravenous TXA [12].

The use of oral TXA during primary TJA was explored recently. The study by Irwin et al. reports on the use of oral TXA during a national shortage of IV TXA. The comparison of the data in their retrospective cohort demonstrated a lower odds ratio for transfusion when oral TXA was used [13]. Fillingham et al. and Kayupov et al. performed similar randomized clinical trials in primary hip and knee arthroplasties comparing a dose of 1 gm IV to 2 gm oral TXA, which demonstrated statistical equivalence with regard to reduction in blood loss and the need for allogeneic blood transfusion [14,15]. A systemic review and meta-analysis by Zhang et al. of six studies demonstrated lower hemoglobin drop, blood loss and transfusion rate in patients receiving oral TXA compared to the placebo group without increasing the risk of complications [16]. Another meta-analysis by the same author Zhang et al. comparing oral versus IV application of TXA concluded that oral TXA is cost efficient and convenient and has similar effects on reducing blood loss and transfusion rate as IV TXA [17].

More recently, the American Association of Hip and Knee Surgeons, American Academy of Orthopaedic Surgeons, Hip Society, Knee Society and American Society of Regional Anesthesia and Pain Medicine worked together to create a clinical practice guideline on the use of TXA in TJA [18]. The efficacy recommendations of the clinical practice guidelines found with a strong recommendation that all formulations (IV, topical and oral) TXA are superior to placebo and equivalent amongst each other in terms of blood sparing properties [18]. Additionally, the clinical practice guidelines cited with a strong recommendation that higher doses and/or multiple doses of any formulation of TXA does not provide reduced blood loss and/or risk of transfusion [18]. The only moderate strength recommendation regarding the efficacy of TXA in primary TJA was the recommendation in favor of the pre-incision dosing of IV TXA [18].

Given the overwhelming literature supporting the blood conservation properties of TXA, we conclude that all formulations and dosing regimens are effective in minimizing blood loss and reducing the need for allogeneic blood transfusions in primary hip and knee arthroplasties.

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QUESTION 6: Does the use of tranexamic acid (TXA) reduce blood loss and need for allogeneic blood transfusion during revision total joint arthroplasty (TJA)?

RECOMMENDATION: Yes. The administration of TXA during revision TJA reduces blood loss and the need for allogeneic blood transfusion.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 97%, Disagree: 0%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

It is well-known that revision TJA cases are more complex and are associated with a greater amount of blood loss and an increased need for allogeneic blood transfusion compared to primary TJA. Despite the vast body of literature investigating TXA following primary TJA, only a limited number of studies exist on the use of TXA after revision TJA. Among the nine published studies, seven are retrospective comparisons with one prospective non-randomized study and only a single randomized clinical trial [1–9]. All seven retrospective comparison studies and the single prospective non-randomized study have shown that intravenous (IV) TXA decreased both the rate of blood transfusion and the amount of blood transfused when compared to controls [1–8]. Wu et al. performed a randomized clinical trial comparing IV verses combined IV and topical TXA in revision total hip arthroplasty (THA), which demonstrated improved blood sparing properties for combined IV and topical TXA [9].

Despite the lack of multiple randomized clinical trials, several retrospective studies have supported the use of TXA to reduce blood loss and transfusion during revision TJA. Despite the known efficacy of TXA in primary TJA, the literature lacks robust evidence in revision TJA. As a result, the recommendation is only provided a moderate level of strength.

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QUESTION 7: Does the use of tranexamic acid (TXA) reduce the incidence of surgical site infection/periprosthetic joint infection (SSI/PJI) following orthopaedic procedures?

RECOMMENDATION: The administration of TXA potentially reduces the incidence of SSI and/or PJI following total joint arthroplasty (TJA) by limiting postoperative anemia and the need for allogeneic blood transfusion.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 89%, Disagree: 5%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Allogeneic blood transfusions are associated with an immunomodulating effect on the host. The immunomodulation properties of allogeneic blood was recognized in 1970s when patients undergoing renal transplant had a better survival if they had received an allogeneic blood transfusion prior to transplantation [1]. By extrapolation one would expect a higher rate of infection in patients who receive allogeneic blood transfusion. A clear link between allogeneic transfusions and infection following primary TJA has not been demonstrated. There are conflicting findings amongst various studies [2–5].

The published studies do, however, support a connection between preoperative anemia and the increased risk of SSI and PJI after TJA [6–8]. Although the literature demonstrates preoperative anemia as a risk factor for allogeneic blood transfusion, we are uncertain about the root cause of the association between anemia and

infection [9]. The increased infection risk in patients with preoperative anemia could be related to higher rate of allogeneic transfusion in this cohort and may be many other factors. It is also possible that preoperative anemia could be a marker of poor host status. However, no literature is available to support a relationship between postoperative anemia and an increased risk of SSI or PJI. It remains uncertain whether a patient with a normal preoperative hemoglobin concentration who experiences postoperative anemia without receiving a transfusion is at an increased risk of SSI or PJI.

Although no studies exist directly linking the use of TXA with a reduction in SSI or PJI after TJA, it is well-established the use of TXA reduces the risk of blood loss and the need for allogeneic blood transfusion. Based on the potential links between allogeneic transfusions or anemia with infection, we extrapolate that any method of blood sparing could assist with reducing the incidence of SSI and PJI.

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1.18. PREVENTION: WOUND MANAGEMENT

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QUESTION 1: Does the type of wound closure (technique and material) affect the incidence of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: There is a lack of strong evidence clearly demonstrating the superiority of any wound closure method following total joint arthroplasty (TJA). The majority of the high-quality studies demonstrate no difference between the various types of wound closure.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 90%, Disagree: 8%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Currently there are several techniques available for wound closure following TJA, including staples, sutures, adhesives and transdermal systems [1]. Although several randomized clinical trials (RCTs) are available, surgeons primarily select wound closure systems based upon personal preference. The ultimate goal is to use a wound closure system that balances cosmetic appearance, clinical outcomes and cost-effectiveness. Based on the currently-available literature, no closure system has been shown to consistently reduce the risk of SSI/PJI. Despite several level I evidence studies investigating the complications of wound closure systems, they are dramatically underpowered. Below is a summary of the available literature on each method of wound closure.

Conventional Suture and Staples

Historically, TJA wound incisions have been closed using nylon sutures or metal staples. Both options have demonstrated low wound complication rates, easily reproducible application and cost-effectiveness, but require a clinic visit within two weeks of surgery for removal [2]. Many studies have comparatively evaluated outcomes following closure with conventional sutures and staples with inconsistent results. Several RCTs and a retrospective study have reported no significant difference in wound complication rates between sutures and staples [2–7]. Other studies have reported superior outcomes for staple closures, while others have reported an increased incidence of infection with staple closures [8–13].

Barbed Sutures

Barbed sutures have been popularized for eliminating the need for knots while demonstrating superior water-tight closures in cadaveric models [14]. Similar to conventional closure techniques, barbed suture has been evaluated in numerous retrospective studies and RCTs with inconsistent results when compared to conventional closures [15–26]. Likewise, the published meta-analyses on barbed suture closure have provided inconsistent results. The meta-analysis by Zhang et al. reported significantly fewer complications and superficial infections when the arthrotomy, subcutaneous and subcu-

ticular tissues are closed with barbed sutures [27]. A meta-analysis by Meena et al. has indicated a higher rate of infection for barbed sutures, albeit not statistically significant [28]. However, another meta-analysis by Borzio et al. confirmed the cost savings associated with barbed sutures but demonstrated no significant difference in complication rates between conventional and barbed sutures [29].

Non-invasive Skin Closure (e.g., Adhesives, Transdermal Systems)

Currently there are two categories of non-invasive skin closure: adhesives and transdermal systems. The majority of RCTs have demonstrated no difference in cosmetic and clinical outcomes between sutures, staples and adhesive closures [4,6,30]. In the Cochrane review by Dumville et al., the effects of various tissue adhesives were compared with sutures, staples and other methods of skin closure techniques using wound infection and dehiscence as the two outcome measures [31]. The results demonstrated no difference in the risk of wound infection between the closure methods, however, there was wide variability in the definition of wound infection between studies. Regarding wound dehiscence, conventional sutures were significantly better than tissue adhesives, but the analysis relied heavily on low-evidence studies.

Only limited evidence exists on the performance of transdermal closure systems. Ko et al. compared outcomes between staples and a transdermal closure in a small cohort of total knee arthroplasty (TKA) patients, which reported no complications, improved cosmesis and reduced pain scores at time of removal [32]. Similarly, Carli et al. assessed a prospective series of TKA patients that found the transdermal closure cohort avoided home care and had fewer complications than the staple cohort [33].

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QUESTION 2: What is the role for vacuum-assisted incisional dressings (iVAC) in orthopaedic patients?

RECOMMENDATION: Prophylactic iVACs appear to be a reasonable option for improved wound healing and decreasing the infection rate in orthopaedic patients at risk for such complications. Prophylactic iVACs used routinely in uncomplicated cases do not appear to provide benefit and lead to increased costs. Lastly, evidence suggests that iVACs may also play a role in resolving some cases of early, benign postoperative drainage.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 85%, Disagree: 11%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Wound management through the application of negative pressure has been used for decades in multiple surgical disciplines, including plastic surgery, general surgery, trauma surgery, cardiothoracic surgery and orthopaedic surgery. It is thought to act through several mechanisms that result in wound contraction, stimulation of epithelial growth and prevention of fluid collection and wound drainage [1].

Within orthopaedic surgery, the use of iVACs has been investigated in studies spanning multiple sub-disciplinary areas, with moderate-strength evidence suggesting that iVACs may benefit wounds in at-risk patients. In retrospective studies, vacuum assisted incisional dressings were associated with fewer wound complications, deep infections and reoperation than standard surgical dressings following treatment of periprosthetic hip and knee fractures [2]. Similarly, incisional negative-pressure wound therapy (iNPWT) dressings were associated with improved wound healing and fewer surgical site infections following revision total hip or knee arthroplasty (THA/TKA), but there was no difference in wound dehiscence, deep infection or reoperation [3,4]. Similar results were observed when iNPWT was used following total ankle arthroplasty [5], long-segment thoracolumbar fusions [6] and high-risk musculoskeletal oncologic wounds [7]. Two prospective randomized controlled trials have also explored the use of iNPWT in high risk orthopaedic trauma wounds. In industry-funded research, Stannard et al. demonstrated a significant reduction in total infections when iNPWT was used after severe open tibia fractures [8] and high-risk lower extremity fractures (calcaneus, pilon and tibial plateau fractures) [9].

Additionally, evidence suggests that iNPWT decreases postoperative hematoma and seroma size and the time to a dry wound. Multiple prospective randomized controlled trials have further shown that iNPWT decreases hematoma/seroma size and the time to a closed dry wound following high-energy trauma [10], hemiarthroplasty [11], THA [12] and spine fracture care [13]. While there is strong evidence that iNPWT has a causal effect on known risk factors for infection (e.g., persistent hematoma or seroma, continued wound drainage), none of these trials were adequately powered to assess for differential infection rate in wounds treated with iNPWT versus standard surgical dressings.

IVACs, however, do not appear to provide a clinical benefit in routine cases. A retrospective study by Redfern et al. demonstrated no difference in superficial or deep infection rates with the use of iVACs in primary THA and TKA [14]. Three prospective randomized controlled trials have studied the use of iNPWT to prevent infection following standard closure in trauma or arthroplasty. Crist et al. found no difference in the rate of deep infection when iNPWT was used after open reduction internal fixation (ORIF) of uncomplicated acetabular fractures [15]. Similarly, there was no difference in wound healing or wound complications between iNPWT in standard surgical dressings after routine THA or TKA [16,17]. In addition, in routine cases, iVACs incur unnecessary additional cost and may cause iatrogenic problems such as skin blistering [18,19].

Lastly, evidence suggests that iVACs may also play a role in resolving some cases of early, benign postoperative drainage.In a retrospective study of the use of iVACs for 109 patients with benign early postoperative drainage after hip arthroplasty, Hansen et al. found that the intervention halted wound drainage without further surgery in most cases and did not find increased complications specific to the device [20].

In conclusion, the use of iVAC dressings are a reasonable option in orthopaedic patients at risk for wound healing complications and may decrease such complications in such patients. The use of iVACs in all cases is likely unnecessary. In addition, iVACS may also play a role in resolving some cases of early, benign postoperative drainage [11].

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QUESTION 3: Do antibacterial-coated sutures reduce the risk of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: The use of antibacterial-coated sutures reduces the risk of SSI following colorectal surgery, however, there is no conclusive evidence that its use reduces the risk of subsequent SSI/PJI in orthopaedic patient populations.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 3%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The risk factors for SSI are multifactorial [1]. The presence of suture material, considered a prosthetic implant, logarithmically reduces the number of organisms needed for SSI from 10^5 to 10^2 colony-forming units and therefore increases the rate of a SSI [2]. Triclosan, a broad-spectrum antibacterial agent against gram-positive and gram-negative bacteria, has been effectively used in suture material since 2003 to reduce SSI [3,4]. Triclosan-coated sutures (TCS) can create an "active zone" around the suture, inhibiting *Staphylococcus aureus*, *Staphylococcus epidermidis* and methicillin-resistant strains of Staphylococci (MRSA and MRSE), *Escherichia coli* and *Klebsiella pneumoniae* from colonizing on the suture for a minimum of 48 hours in in vitro studies [5,6].

TCS have been reported to reduce SSI in many surgical disciplines. In a randomized controlled trial of colorectal surgery, the use of TCS had a significantly lower incidence of wound infection compared with the use of non-antimicrobial sutures (4.3% vs.9.3%) [7]. In a meta-analysis with level I evidence, no publication bias and a robust sensitivity analysis, the use of TCS provided a reduction of approximately 30% in a population of 5,000 patients after various clean, clean-contaminated and contaminated surgeries [8]. A recent systematic review and meta-analysis included 21 RCTs (6,462 patients) with various surgery types (colorectal, head and neck, abdominal, cardiac and vascular and general surgery) and showed SSIs were reduced significantly by the use of TCS compared with uncoated sutures (relative risk (RR): 0.72, 95% confidence interval (CI) 0.60 to 0.86, $p < 0.001$) [9].

Current clinical guidelines have contradictory suggestions for TCS. The World Health Organization (WHO) [10] and The National Institute for Health and Care Excellence (NICE) [11] support the use of TCS for the risk reduction of SSI. The Infectious Diseases Society of America (IDSA) [12] and The Society for Healthcare Epidemiology of America (SHEA) [13] are against its routine use. The recent Centers for Disease Control and Prevention (CDC) guideline supports consideration of TCS use for the prevention of SSI, balancing clinical benefit and harm [14].

There is little evidence assessing the efficacy of TCS on SSI following total joint arthroplasty (TJA). To our knowledge there has been 1 prospective study involving 2,546 patients undergoing elective TJAs at 3 hospitals [15]. A total of 1,323 patients were randomized to a standard suture group, and 1,223 to the TCS group with SSI at 30 days postoperatively as a primary end-point. Sprowson et al. reported that the rates of superficial SSI were 0.8% in the control group and 0.7% in the TCS group ($p = 0.651$). The rates of deep SSIs were 1.6% in the control group and 1.1% in the TCS group ($p = 0.300$). The rates of deep and superficial SSIs were 2.5% in the control group and 1.8% in the TCS group ($p = 0.266$).

Based on the above level I studies on various types of surgeries and surgical wounds, the use of TCS seems to reduce the rate of SSI.

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QUESTION 4: Does the use of topical incisional sealants (i.e., integuseal, dermabond, etc.) reduce the incidence of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI) in patients undergoing orthopaedic procedures?

RECOMMENDATION: While we recognize that the use of topical incisional sealants has the potential to reduce wound drainage, there is no evidence that the use of such products has any impact on the incidence of SSI/PJI.

STRENGTH OF THE RECOMMENDATION: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Commercially-available topical incisional sealants (Integuseal, Dermabond, Liquiband and others) aim to add strength and integrity to wound closure and, by sealing the wound, may reduce the incidence of wound drainage. With the creation of an impervious mechanical barrier at the incision, these products are believed to reduce the entry of infecting organisms into the deeper tissues and the potential for subsequent SSI/PJI. These products can be convenient to use, as they may reduce the need for placement and removal of sutures and staples. These products remain popular in a variety of surgical specialties.

Some of the products have also demonstrated bactericidal activities against gram-positive bacteria in vitro [1]. However, effectiveness in preventing surgical site infection remains in question. To date, randomized studies across surgical subspecialties have not shown significant reductions in infection rate with the use of these products. Two recent systematic reviews were conducted evaluating the effectiveness of adhesive sealants across multiple surgical specialties, primarily outside of orthopaedics.

In 2010, 14 randomized clinical trials (1,152 patients) were published to determine the relative effects of various tissue adhesives and conventional skin closure techniques on the healing of surgical wounds. Only one of these studies was in the field of orthopaedics. This study demonstrated that sutures were significantly better than tissue adhesives for minimizing dehiscence (10 trials). There was no difference between low viscosity and high viscosity adhesives in respect to dehiscence. Surgical procedures that were described by the studies were diverse and included hand surgeries, blepharoplasty, circumcision and excision of benign skin lesions. None of these trials evaluated incisions around areas of high tension such as the knee.

There was no significant difference in the rate of infection comparing sutures and tissue adhesives. However, no study reported an a priori calculation for the sample size and this may be relevant [2].

In 2014, another update of the previous study identified 19 additional eligible randomized clinical trials resulting in a total of 33 studies (2,793 patients). There was low-quality evidence that sutures were significantly better than tissue adhesives for reducing the risk of wound breakdown (dehiscence, rate ratio (RR): 3.35, 95% confidence interval (CI) 1.53 to 7.33, 10 trials, 736 participants that contributed data to the meta-analysis). For other outcomes such as infection rate, patient and operator satisfaction and cost, there was no evidence of a significant difference for either sutures or tissue adhesives. Eighteen trials that compared the use of tissue adhesives with sutures reported wound infection data, however, as eight of these had no cases of infection, only data from the remaining ten studies contributed to the meta-analysis. The studies included for this review did not demonstrate any significant difference in the proportion of infections in incisions closed with tissue adhesives compared with other conventional techniques. No study reported an a priori calculation for the sample size, and this may be relevant. Even the largest of the studies would have been unlikely to have been adequately powered to show any significant difference given the relatively low incidence of wound infections following many types of surgery [3].

Recent SSI prevention guidelines from the World Health Organization (WHO) state that, “antimicrobial sealants should not be used after surgical site skin preparation for the purpose of reducing SSI” [4]. A Cochrane review also found that “sutures were significantly better than tissue adhesives for minimizing wound

dehiscence" and there was no difference in the SSI when skin adhesives were used [2,3].

The effect of 2-octyl cyanoacrylate (Integuseal) on SSI was evaluated in randomized trials in sternotomy [5,6], colorectal [7] and trauma surgery wounds [8]. A prospective study found that 2-octyl cyanoacrylate reduced the rate of SSI versus the use of staples for skin closure in spinal surgery [9]. The use of Integuseal was also shown to decrease the incidence of SSI in cardiac surgery in another prospective study [10]. Non-randomized data in orthopaedics has evaluated its use in arthroplasty [11] and scoliosis [12] surgery. The arthroplasty study was a single-arm, single-surgeon series of 360 patients with a 0.8% rate of superficial SSI, no PJI and a single case of contact dermatitis.

Data on patients undergoing orthopaedic procedures on the use of Dermabond have not revealed differences in SSI/PJI rates. One randomized trial found no difference in scar cosmesis or infection rate [13], and another two studies found decreased wound drainage with the use of Dermabond, but no difference in SSI/PJI rate [14,15]. No trial was adequately powered to detect a difference. In a large historical control study of hip and knee arthroplasty patients, no differences in infection rate were noted at six-week follow-up [16]. A randomized controlled trial for skin closure after scheduled cesarean delivery demonstrated similar results using Dermabond or a monofilament synthetic suture [17].

Hypersensitivity reactions to these organic sealants are rare, but can be serious [18–22]. A recent report of three patients with blistering periincisional contact dermatitis was found [21,22].

Given the presence of extensive data in other surgical subspecialties suggesting that topical adhesives do not lower surgical infection rates, the lack of data suggesting efficacy in orthopaedics and the rare but serious hypersensitivity reactions to these agents, we cannot recommend the routine use of incisional sealants for the purpose of prevention of SSI/PJI in patients undergoing orthopaedic procedures.

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QUESTION 5: Does the use of surgical suction drains increase the risk of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: There is no direct evidence to suggest that the use of surgical drains (for < 48 hours) leads to an increase in the rate of subsequent SSI/PJI. The use of surgical drains lead to a higher volume of blood loss and an increased need for allogeneic blood transfusion, which may indirectly increase the rate of SSI/PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 7%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

In orthopaedic surgery, the use of surgical drains has been most extensively evaluated in the subspecialty of hip and knee arthroplasty. Most of the studies regarding the use of surgical drains in hip and knee arthroplasty have focused on its effect on blood loss, on the need for transfusions and on their effectiveness in preventing subsequent wound healing complications including PJI and SSI. The purpose of surgical drains is to optimize wound healing by reducing fluid (blood) accumulation in the surgical site. This may be related to several advantages including decreased tissue swelling and skin tension, which improves skin perfusion and decreases wound complications [1–5], reduced postoperative pain and enhancing recovery [2,5–7] and potentially lower the risk for infection as the hematoma is believed to interfere with the body's defense mechanisms [7,8].

In a systematic review of the Cochrane database, Parker et al. investigated the utility of closed suction drainage after orthopaedic surgery [9]. The investigation involved 36 studies involving 5,697 surgical wounds and did not find benefit to the use of drains. Some of the outcomes specifically investigated were infection, wound complications, hematoma formation and reoperation. The authors found no difference in the majority of the outcomes between cases with surgical drains and those without surgical drains. The only difference was found in the blood transfusion requirement with drains leading to a greater rate of transfusion. The use of drain reduced the rate of ecchymosis around the incision, the only benefit attributed to the use of surgical drain.

Additional studies illuminated on the incidence of superficial wound infections (Table 1). Only one study by Zeng et al. [7] found a significantly lower rate of wound infection in patients undergoing primary total hip arthroplasty (THA) in whom a surgical drain was used versus those without a surgical drain. However, a pooled analysis found an elevated superficial infection rate in the non-drainage group (rate ratio (RR): 0.76, 95% confidence interval (CI) 0.574 to 1.017, p = 0.045). No significant differences in the prevalence of superficial wound infections were noted when studies for THAs and total knee arthroplasties (TKAs) were examined separately (Tables 2 and 3). The duration of drainage was not found to be related to the rate of superficial wound infection, which was 3.3% for the entire cohort and for both arthroplasties types (RR: 1, 95% CI 0.823 to 1.220, p = 1). Yet, when reviewing the influence of drainage duration on TKAs by itself, a longer drainage period was found to be related to increased superficial wound infection rates (2.1% vs. 0%). No similar effect was found for total hip replacements (Table 4).

TABLE 1. Results for total hip and total knee arthroplasties

	Studies Included		Cohort	N (%)	p value
Blood transfusion (patients)	7	Drainage	679	190 (28.0)	0.013
		No-drainage	585	127 (21.7)	
Superficial wound infection	13	Drainage	987	28 (2.8)	0.045
		No-drainage	883	39 (4.7)	
Deep wound infection	13	Drainage	987	8 (0.8)	0.185
		No-drainage	883	13 (1.6)	
Length of stay	6	Drainage	613	6.9±3.3	0.871
		No-drainage	575	6.6±3.3	

TABLE 2. Results for total knee arthroplasty

	Studies Included		Cohort	N (%)	p value
Blood transfusion (patients)	3	Drainage	211	67 (31.8)	0.794
		No-drainage	100	30 (30)	
Superficial wound infection	13	Drainage	410	4 (1.0)	0.727
		No-drainage	296	4 (1.4)	
Deep wound infection	13	Drainage	410	3 (0.7)	0.104
		No-drainage	296	7 (2.4)	

TABLE 3. Results for total hip arthroplasty

	Studies Included		Cohort	N (%)	p value
Blood transfusion (patients)	4	Drainage	468	123 (26.3)	0.026
		No-drainage	485	97 (20)	
Superficial wound infection	13	Drainage	577	24 (4.2)	0.110
		No-drainage	537	35 (6.5)	
Deep wound infection	13	Drainage	577	5 (0.9)	0.767
		No-drainage	537	6 (1.1)	

TABLE 4. Results for duration of drainage, total hip and total knee arthroplasties

		Studies Included		Cohort	N (%)	p value
Blood transfusion (patients)		5	24 hours	476	104 (21.8)	< 0.001
			48 hours	98	53 (54.1)	
Superficial wound infection	All	10	24 hours	679	22 (3.3)	1
			48 hours	187	6 (3.3)	
	Knee	6	24 hours	268	0 (0)	0.004
			48 hours	92	4 (2.1)	
	Hip	4	24 hours	411	22 (5.4)	0.282
			48 hours	95	2 (2.1)	
Deep wound infection	All	10	24 hours	679	2 (0.3)	0.006
			48 hours	187	5 (2.7)	
	Knee	6	24 hours	268	0 (0)	0.016
			48 hours	92	3 (3.3)	
	Hip	4	24 hours	411	2 (0.5)	0.162
			48 hours	95	2 (2.1)	

TABLE 5. Characteristics of the studies

Author	Year	Procedure	No. of Wounds With Drainage	No. of Wounds Without Drainage	Mean Age	Male Patients (%)	Length of Follow-Up (Months)
Abolghasemian [3]	2016	Revision TKA	42	41	NA	38 (47)	3
Fichman [16]	2016	Revision THA	44	44	68	40 (45)	1.5
Suarez [18]	2016	Primary THA	59	61	63	60 (52)	1.5
Koyano [2]	2015	Bilateral TKA	51	51	NA	NA	1*
Zhang [14]	2015	Primary UKA	48	48	67	28 (30)	18.3
Zeng [7]	2014	Primary THA	83	85	60	81 (48)	3
Li [19]	2011	Primary TKA	50	50	63	26 (34)	12
Omonbude [11]	2010	Primary TKA	40	38	NA	NA	1.5
Seo [15]	2010	Primary TKA	111	0	73	6 (5)	12
Strahovnik [5]	2010	Primary THA	97	42	66	46 (33)	3
Walmsley [12]	2005	Primary THA	282	295	68	213 (39)	36
Esler [17]	2003	Primary TKA	50	50	73	45 (45)	NA
Kim [13]	1998	Bilateral TKA	69	69	64	10	12

THA, total hip arthroplasty; TKA, total knee arthroplasty; UKA, unicompartmental knee arthroplasty

* No specific follow-up duration was mentioned yet a complication following one month was noted.

** Only patients in the non-proteinase inhibitor groups were included.

Regarding deep wound infections, the literature shows that the use of a surgical drain in general was not related to increased rates of deep infection. None of the 13 included studies have reported a significant difference in the incidence of deep wound infections (Table 5). Likewise, the pooled results have also failed to demonstrate a significant difference between groups and for THAs and TKAs separately. The rate of deep infection was 1.5% in total, 0.8% for wounds treated with drains and 1.6% for wounds left without drains (RR: 0.7, 95% CI 0.405 to 1.210, p = 0.185) (Table 1). Deep infection rates were 1% (0.9% and 1.1% for the drainage and non-drainage groups) and 1.4% (0.7% and 2.4% for the drainage and non-drainage groups) following THAs and TKAs respectively (Tables 2 and 3).

A sub-analysis was performed on the influence of drainage duration on infection rates which found that a longer drainage duration was significantly related to increased deep infection rates. This correlates with results of others who showed increased positive cultures from drainages who were left inside the wound for longer periods [4,10]. The duration of time in which the drainage was left in the wound was stated in 10 studies [3,5,7,11–17], and was either 24 or 48 hours (in 1 study [11] the average duration was 20 hours with a range of 15 to 26 hours, and was added to the 24-hour group for analysis). A longer duration of wound drainage was found to be significantly related to increased rate of deep wound infection, as the prevalence of deep wound infection was 2.7% in the 48-hour group and only 0.3% in the 24-hour drainage group (RR: 0.363, 95% CI 0.1123 to 1.1702, p = 0.006). This was also true for a pooled analysis for the total knee arthroplasty group (six studies included, p = 0.016), but not for the total hip arthroplasty group (four studies included, p = 0.162) (Table 4). It can be summarized that both deep and superficial infection rates were insignificant when drainage duration was limited to shortened periods of time and with prompt removal.

In general, it was found that surgical drains led to an increased need for blood transfusion. This is important regarding SSI/PJI because blood transfusions are believed to be associated with immunosuppression and postoperative infections rates are reported to be higher following blood transfusion [18,19]. Seven studies provided the number of patients treated with blood transfusions after surgery [7,12,15–17,20,21]. Three studies found the drainage group to require significantly higher transfusion rates [12,16,21]. Likewise, the pooled analysis also found this group to necessitate more blood units, as 28% of the patients in the drainage group were given blood, compared to 21.7% in the non-drainage group (RR: 1.16, 95% CI 1.001 to 1.238, p = 0.013) (Table 1). Separate analysis for THAs including 4 studies also found the number of patients requiring blood transfusions to be higher in the drainage group (26.3% vs. 20% for the other group, RR: 1.19, 95% CI 1.032 to 1.367, p = 0.026). No similar effect was found for TKAs (Tables 2 and 3).

Many of the aforementioned randomized controlled studies have investigated the use of surgical drains in the setting of hip and knee arthroplasty. It has been established that for most measures, there are no differences when comparing drains to no drains, except increased blood loss and transfusion requirements. Many of these studies have investigated whether drains decrease wound complications and SSI/PJI and they have universally shown no difference, in turn showing that surgical drains do not appear to increase the risk of subsequent SSI/PJI when used for a shortened duration of time.

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QUESTION 6: What surgical dressing (i.e., occlusive, silver impregnated, dry gauze) is associated with a lower risk of surgical site infection/periprosthetic joint infection (SSI/PJI) in patients undergoing orthopaedic procedures?

RECOMMENDATION: Occlusive and/or silver-impregnated dressings have been proven to reduce the rate of wound complications, SSI and PJI compared to standard gauze dressings and should be considered for routine use. The majority of the literature at present focuses on total joint arthroplasty (TJA). However, further research is required to see if the added antimicrobials (such as silver), the occlusive, active-nature of the dressing or their combination is responsible for the demonstrated reduction in SSI/PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 81%, Disagree: 12%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

To successfully prevent SSI and PJI, the patient must be optimized before, during and after orthopaedic surgery. One method of infection prevention gaining recent attention is the type of post-surgical dressing. Wound complications are common after orthopaedic procedures. These are particularly important in TJA as patients are encouraged to mobilize early and often and wounds are over mobile areas such as the knee joint. Appropriate prevention and management is crucial since wound issues can lead to PJI if left untreated [1]. While traditional gauze and tape dressings have been used after surgical procedures for decades, new commercial dressings have questioned this practice [2–4].

Dressings have been classified as passive (gauze, absorbent pads, adhesive tapes, island dressings), active (films, hydrocolloid, hydrofiber, alginate, foam) and interactive (antimicrobial, biomaterial, larva therapy, vacuum dressings) [5]. Passive dressings only serve a protective function, while active dressings promote healing through the creation of a moist environment. Interactive dressings interact with the wound bed to further enhance healing and include, for example, antimicrobial agents (such as silver). An increasing body of literature supports use of a dressing that provides an impermeable barrier to pathogens and preserves a moist environment. Good fluid management capacities are important to prevent excess exudate, which causes maceration and to reduce the frequency of dressing changes thereby reducing the risk of exposure to outside pathogens [5]. While many studies have compared various dressings and the rate of wound complications (defined as blisters, erythema, maceration, leakage) or fluid handling capacity (wear time, mean dressing changes) [5], few have been adequately powered to investigate rates of SSI and PJI [6–12]. Sharma et al. [5]. recently performed a systemic review and meta-analysis on 12 randomized controlled trials (RCTs) [6–17] comparing alternative dressing materials for postoperative management of wounds following TJA. Eight of these studies reported SSI data but no dressing type was superior over another in SSI reduction. However, occlusive film dressings (odds ratio (OR): 0.35, 95% confidence interval (CI) 0.21 to 0.57) or occlusive dressings with hydrofiber (OR: 0.28, 95% CI 0.20 to 0.40) were significantly less likely to have wound complications than those managed with passive (standard) dressings [5]. The authors concluded that there was insufficient evidence available to determine whether the use of these advanced dressings reduced PJI.

Recently, two interactive dressings are gaining popularity. One is the Aquacel® Ag surgical dressing (ConvaTec) that both maintains a moist environment through use of a weaved cellulose center (hydrofiber) that allows it to contour to the skin and prevents the growth of microorganisms by releasing antimicrobial ionic silver when in contact with fluid [18,19]. Another is the Silverlon® Surgical Dressing (Argentum Medical) with a woven nylon dressing that is silver plated and embedded in a waterproof foam adhesive [20]. Three large cohort, case-controlled studies have retrospectively investigated the utility of these dressings for PJI reduction after TJA. All three studies used the Musculoskeletal Infection Society (MSIS) criteria for PJI [18–20]. Cai et al. compared 903 patients receiving an Aquacel Ag dressing (removed at 5 days) to 875 receiving a standard xeroform and gauze dressing removed at 2 days postoperatively after TJA [19]. They reported an acute PJI rate (within 3 months of surgery) of 0.44% in the Aquacel Ag dressing group compared to 1.7% in the standard gauze dressing group ($p = 0.005$).

A multivariate analysis revealed that use of Aquacel dressing was an independent risk factor for reduction of PJI (OR: 0.165, 95% CI 0.051 to 0.533, $p = 0.003$) [19]. These results were corroborated by Grosso et al. who compared 605 patients with Aquacel Ag dressing (removed at 7 days) to 568 xeroform and gauze dressings (removed at 2 days and changed every other day) after TJA [18]. The incidence of acute PJI for patients managed with a sterile xeroform dressing was 1.58% (9/568). The incidence of PJI for patients managed with the use of Aquacel dressing was 0.33% (2/605, $p = 0.03$). Similar to Cai et al., a multiple logistic regression demonstrated use of an Aquacel dressing as a protective factor for PJI (OR: 0.092, 95% CI 0.017 to 0.490, $p = .005$) [18]. Tisosky et al. evaluated 309 patients with the Silverlon dressing (removed at 7 days) compared to 525 patients with xeroform and gauze (removed at 2 days) after TJA [20]. They found an overall infection rate of 8.4% in the control group versus 3.90 % in the Silverlon group (OR: 0.38 95% CI 0.25 to 0.58, $p = 0.012$). There was no PJI in the Silverlon group vs.12 (2.3%) in the control ($p = 0.007$). In addition, the superficial infection rate was 6.1% in control vs. 3.9% in Silverlon (OR: 0.54, 95% CI 0.34 to 0.87, $p = 0.011$). In a multivariate logistic regression the Silverlon dressing was independently associated with decreased infection (OR: 0.39, 95% CI 0.27 to 0.57, $p < 0.0001$) [20]. Finally, Kuo et al. performed a prospective, RCT comparing the Aquacel Ag to a standard dressing in 240 TKA patients [21]. They found that the Aquacel Ag dressing was independently associated with a reduction in SSI (as defined by the Centers for Disease Control and Prevention (CDC) [22]) when controlling for confounding variables (OR: 0.07, 95% CI 0.01 to 0.58, $p = 0.01$) [21].

In conclusion, active and interactive dressings have been shown to reduce the rates of SSI and PJI after joint arthroplasty compared to passive dressings. The benefit of adding antimicrobial/antiseptic agents such as silver or 0.2% polyhexamethylene biguaide [23] in

postoperative dressings is still controversial as few studies have compared active dressings to interactive dressings [24]. In addition, studies investigating the use of active or interactive dressings in foot and ankle surgery [25], hip fracture surgery [26] and spinal fusion [27] are limited and have not demonstrated a reduction in SSI. Finally, formal cost-effectiveness studies will be needed to see if the increased price of the occlusive, silver-impregnated dressings (USD $30 to $40) [19,20] compared to standard dressings (USD $2 to $5) is justified for routine versus selective use by the reduction in cost with decreased SSI/PJI.

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QUESTION 7: When should sterile surgical dressings be removed and how frequently should subsequent dressings be changed following orthopaedic procedures?

RECOMMENDATION: The dressing placed over the surgical wound under sterile conditions in the operating room should be changed based on saturation of the dressing. Early removal and frequent changes of the surgical dressing are not needed if there is no significant bleeding or drainage on the original dressing. If the dressing remains dry, wound coverage for a minimum of 48 hours has been recommended.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 97%, Disagree: 3%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Sterile dressings are applied to the skin following primary closure in most orthopaedic surgery. Dressing acts as a physical barrier, which protects the wound from contamination until the continuity of the skin is restored [1]. The first phase of the wound healing cycle is the hemostasis phase, during which the continuity of the skin is restored. In the clean wound, with regular edges following incisions,

the wound is usually closed within 48 hours [2]. The general practice is to cover surgical incisions post procedure to control postoperative bleeding, to absorb exudates and to provide protection [3]. The ideal dressings produce a moist, warm and clean environment that promotes wound healing [4,5]. However, the moist environment created by a dressing left on the wound for a longer period could increase the risk of maceration, leading to weakening of the tissue and wound [6].

Concerning the prevention of surgical site infections (SSIs), the ideal timing of dressing removal is an unresolved issue. Some professionals prefer to leave wounds uncovered from the moment of closure, others uncover them after a certain time and still others keep them covered until suture removal [3]. Clinical guidelines from the Centers for Disease Control and Prevention (CDC) and the British National Collaborating Centre for Women's and Children's Health (the latter commissioned by the National Institute for Health and Clinical Excellence in 2008) mainly recommend covering surgical incisions with a dressing for a period of at least 48 hours postoperatively. Uncovered or early exposed wounds seem to be associated with an increased risk of contamination and SSIs, but some studies suggest that longer dressing periods have no benefits [3]. While an abundance of studies comparing different dressings was available, no meta-analyses or systematic reviews of randomized control trial (RCT) of early vs. late removal of sterile dressings in orthopaedic surgery exist. One RCT comparing removal of a bulky dressing after 2 weeks compared to after 48 to 72 hours following carpal tunnel decompression found no significant difference in wound complication, but the study consisted of a rather small cohort of 94 patients, none of whom developed a SSI [7].

One systematic review on early vs. late dressing removal including all surgical specialties was identified, in which 3 RCTs were included with a total of 280 patients [8]. Participants in the 3 studies were randomized to early dressing removal (< 48 hours following surgery) or delayed dressing removal (continued dressing for > 48 hours following surgery). The primary outcome was surgical site infection as defined by Horan [9]. There was no significant difference in the proportion of people who developed superficial SSI between the early and delayed dressing removal groups. No deep SSI or deep dehiscence was reported in the early or in the delayed dressing removal groups [8].

In addition to the systematic review, two randomized controlled trials were identified, which investigated the effect of early removal of wound dressing on the risk of infection. The primary outcome for both studies was SSI. Heal et al. compared removing the dressing within the first 12 hours with leaving the dressing on for the first 48 hours and found no statistically significant difference in the incidence of surgical site infection [10]. In a similar study, Chrintz et al. compared removal of dressing after 24 hours with keeping the wound dressed until removal of the sutures and found no statistically significant difference in the incidence of surgical site infection [11].

If the dressing is disturbed less often, the risk of infection is reduced and this aids the healing process [12]. Every time a dressing is changed, there is a potential risk for introducing pathogens into the wound, which can subsequently lead to SSI or PJI. Wound dressings keep the wound near core body temperature, which increases the rate of mitotic cell division and leukocyte activity that is necessary for wound healing. When a dressing is changed, it takes three to four hours for the cellular activity of the wound to resume. Hence, episodic cooling associated with dressing changes should be avoided as much as possible. Also, fewer dressing changes protects the wound from repeated exposure to pathogens in the surrounding air [13].

The costs associated with a wound dressing depends on two factors: the unit cost of the dressing and the number of dressing changes required [14]. Fewer dressing changes can decrease the costs.

Dressing changes can also be affected by dressing type. Modern dressings need less frequent changes and can decrease the rate of acute SSI and periprosthetic joint infection (PJI) [15]. Abuzakuk et al. demonstrated that there were less dressing changes for hydrofiber dressings within the first five postoperative days compared to the use of a central pad group. They theorized that leaving the hydro fiber dressing undisturbed for a longer period of time could help prevent wound infections [16]. Hopper et al. showed that, wear time for the traditional dressing (two days) was significantly shorter than for the modern dressing (seven days, $p < 0.001$), and required more changes . They also found that the modern dressing can create less need for dressing changes, thus decreasing burden on healthcare personnel, diminishing superficial wound problems and avoiding delays in hospital discharge due to wound healing issues [17].

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QUESTION 8: Do patients need to refrain from getting a surgical incision wet or submerging it in water to prevent surgical site infection/periprosthetic joint infection (SSI/PJI)? If so, for how long postoperatively?

RECOMMENDATION: Patients need to refrain from getting the surgical incision wet for the first 48 hours after surgery.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 11%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Adequate postoperative wound hygiene is of major importance for prevention of SSI. However, limited literature about postoperative washing is available. Wound re-epithelialization of the incision occurs within 48 hours, although this process can vary among patients [1]. Due to lack of evidence regarding the best manner of managing surgical wounds in the postoperative period, surgeons' instructions to patients for treating surgical wounds vary. A time period of two weeks is widely proposed to prevent contamination of sutures themselves [2], since this is the time frame for staple or suture removal [3].

The 2008 National Institute for Health and Clinical Excellence (NICE) guidelines [4] suggest keeping surgical wounds covered and dry for at least 48 hours after surgery. During this time, wounds may be washed with a sterile saline solution. Only one randomized controlled trial with a relatively low number of 32 patients has evaluated if showering can affect bacterial load after primary total knee arthroplasty (TKA) [5]. Yu et al. evaluated wound colonization by bacteria at various points up to 2 weeks, in 2 groups consisting of 16 patients each. One group was allowed to shower at two days postoperatively and the other group was instructed to wait until two weeks. They reported no statistically significant differences in terms of microorganism prevalence, with no infections noted during the study. Greater patient satisfaction was noted in the early shower group. However, a significant limitation of the study was its small sample size [5]. Hsieh et al. in another clinical trial compared wound-related outcomes following general surgical procedures in 2 equal groups comprising of 222 patients [6]. One group was allowed to get the surgical wound wet at 48 hours after surgery and the other delayed washing until stitch removal. They demonstrated that clean and clean-contaminated wounds can be safely showered 48 hours after surgery. Postoperative showering did not increase the risk of surgical site complications. Increased patient satisfaction and lower cost of wound care are two benefits reported for early wound washing. Heal et al. conducted a large prospective randomized controlled trial for minor skin excisions within general practice [7]. They concluded that wounds can be allowed to get wet in the first 48 hours after minor skin excision without increasing the incidence of infection.

In a systematic review, Dayton et al. found nine randomized clinical trials which showed that there was no reason to avoid showering or bathing the surgical wound as part of routine hygiene during the healing period [8]. In addition, there was no increased risk of surgical wound infection following wound washing at 12 hours after surgery. In two Cochrane database reviews Toon et al. [9] and Chang [10] reported that no conclusive evidence is currently available regarding the benefits or harms of early versus delayed postoperative showering or bathing for the prevention of wound complications. They recommended further randomized controlled trials to compare early versus delayed postoperative showering or bathing.

Several other studies, not directly related to arthroplasty, including general surgical incisions [11], sutured wounds [12], spinal surgical sites [13] and foot and ankle surgeries [14] have failed to demonstrate increased infection rates when early showering was allowed. Nevertheless, published data also demonstrate similar rates of SSI in surgical wounds that remained covered or uncovered and washed with tap water in the first 48 hours following surgery [15,16]. Additionally, cleaning with tap water versus sterile saline was found to have no effect on the incidence of infection [17].

The role of wound submersion in terms of SSI is further complicated by the availability of occlusive dressings, which have gained wide acceptance recently [18]. Dressings that are impermeable to water have been reported to reduce incidence of infection after joint arthroplasty [19–21].

Showering after surgery remains a controversial issue in orthopaedic surgery. A potential harm would be wound-related complications. On the contrary, benefits of early showering would be improvement in quality of life and better rehabilitation outcomes [22].

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QUESTION 9: What is the definition of persistent wound drainage?

RECOMMENDATION: There is no validated definition of "persistent wound drainage." In the absence of such data, we define persistent wound drainage as any continued fluid extrusion from the operative site occurring beyond 72 hours from index surgery.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 78%, Disagree: 17%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Early wound drainage is not uncommon in patients undergoing total joint arthroplasty (TJA), and can be observed in up to 10% of patients [1–3]. Serous or serosanguinous drainage shortly after the procedure is benign and can be explained by the surgical disruption of superficial capillaries. On the contrary, many publications have noted the severity of persistent drainage, which may potentially be a sign of an evolving infectious process [2,4–8]. The previous 2013 International Consensus Meeting on Periprosthetic Joint Infection (ICM) reached a strong consensus that continued drainage after 72 hours postoperatively should be closely monitored and that a wound persistently draining greater than 5 or 7 days after diagnosis should be re-operated on without delay [5]. It is also advisable to refrain from collecting culture samples of the drainage early on, since these will often yield normal skin flora [4].

In a study conducted by Patel et al. composed of 2,437 total hip and knee arthroplasty (THA and TKA) patients, they concluded that every additional day of wound drainage increased the probability of developing a wound complication following THA and TKA, by 42% and 29% respectively [9]. In addition, Galat et al. performed a study of 17,784 patients who underwent primary TKA and discovered that patients who require earlier surgical intervention for wound-healing complications are at a significantly increased risk for additional interventions, such as deep infection surgery, resection arthroplasty, muscle flap coverage or amputation [3].

The difficulty lies in accepting a definition for "persistent drainage" to allow for timely intervention, since literature is not consistent. For instance, in a recent study involving 127 orthopaedic surgeons who replied to wound drainage questionnaires, the highest portion of respondents (36.7%) defined persistent wound drainage as greater than 5 days postoperatively, while other respondents defined the duration as anywhere from greater than 1 day to greater than 14 days postoperatively [10]. Weiss and Krackow were among the first to attempt defining persistent drainage [1]. Several other authors afterward defined persistent wound drainage by time, type of exudate (serous, sanguineous, purulent, etc.), site (wound or from suction drains) and presence of microorganisms from culture. See Table 1 below for a list of predominant definitions that have developed.

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TABLE 1. Literature with definitions of persistent wound drainage

Author	Year	Number of Procedures	Definition	**Additional Notes/ Conclusions**
Weiss [1]	1993	597	1. Drainage for 4 consecutive days after POD 5 2. Drainage that significantly soaks a 2"x 2" gauze dressing 3. Drainage that emanated from the same specific site(s) along the wound	Primary and revision TKA, 1.3% developed persistent drainage
Saleh [6]	2002	2,305	2 days PO for non-infected cases, 5.5 days PO for infected cases.	12.7-times greater risk of SSSI for wounds draining more than 5 days
Jaberi [2]	2008	11,785	Drainage greater than 48 hours post-op that soaks through post-op dressings	Primary and revision TJA, 2.9% developed persistent drainage
Butt [11]	2011	77	Continued drainage beyond POD 4	Primary TKA, periarticular local anesthesia, subvastus approach, and tourniquet time led to less wound drainage
Hansen [12]	2013	109	Continued drainage beyond POD 3 or 4	Primary and revision THA
Parvizi [5] (2013 ICM on PJI)	2013	n/a	Continued drainage from operative site greater than 72 hours post-op	Strong consensus among delegates. Persistent drainage more than 5 or 7 days after diagnosis should be re-operated on without delay.

POD, postoperative day; TKA, total knee arthroplasty; TJA, total joint arthroplasty; SSSI, superficial surgical site infection; ICM, international consensus meeting; PJI, periprosthetic joint infection

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1.19. PREVENTION: POSTOPERATIVE FACTORS

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QUESTION 1: Is early mobilization after orthopaedic procedures associated with an increased risk of wound drainage or surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Current literature reports no increased risk of wound drainage or SSI/PJI with early mobilization following orthopaedic procedures.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Persistent wound drainage after total joint arthroplasty (TJA) is defined as continued drainage from the surgical incision for greater than 72 hours, as this standard allows for earlier intervention and may thus limit adverse consequences [1]. Persistent drainage is an important sign that a surgical wound may become problematic [2,3].

Postoperative incisional drainage occurs in 1% to 10% of patients undergoing primary TJA [4–6]. While drainage requires close monitoring, the majority of cases resolve spontaneously without a need for surgical debridement [7]. Patients with a draining wound on postoperative days two to three should remain in the hospital for close clinical monitoring and they may initially be treated with compressive dry dressings because this typically involves superficial layers [2]. However, as persistent drainage for over 72 hours may represent more serious issues such as fat ischemia or a capsular defect, surgical intervention may be necessary to avoid infectious complications [2].

Physiotherapy, specifically knee range of motion, should be temporarily limited for 24 to 48 hours. Continuous passive motion

should be avoided, or at least limited, as flexion past 40 degrees is known to reduce transcutaneous oxygen saturation about the incision following total knee arthroplasty (TKA) [8]. These limited range of motion parameters have shown no increased incidence of infection when compared to patients treated with complete immobilization [8].

Anticoagulation status should also be reviewed, and it is important to consider short-term cessation of anticoagulation. Hemostasis in the setting of orthopaedic procedures prevents hematoma formation and persistent drainage [2]. Patients treated with low-molecular weight heparin (LMWH) for prophylaxis against deep venous thrombosis have shown longer times to achieve a dry surgical wound, compared to those treated with aspirin and mechanical compression or Coumadin [7]. In light of this, it is prudent to temporarily stop anticoagulation with LMWH, or other chemical anticoagulation, but continue mechanical venous thromboembolism prophylaxis.

Based on the review of literature related to persistent wound drainage, we have found no evidence that links early mobilization of the patient with an increased risk of wound drainage and/or infection. Considering the fact that early ambulation of the patients in extremely useful to prevent complications such as venous thromboembolism and improve patient outcome, we still feel that early ambulation stands to benefit the patient while having minimal to no adverse effects.

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QUESTION 2: Is it necessary for a patient to postpone having an invasive dental procedure after total joint arthroplasty (TJA)?

RECOMMENDATION: In the absence of evidence, we recommend that non-urgent invasive dental procedures, if possible, be delayed until osseointegration of uncemented components are complete.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 82%, Disagree: 10%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

Hematogenous periprosthetic joint infection (PJI) occurs when bacteria are seeded to the prosthesis via the bloodstream from a distant anatomic source. It has been estimated that hematogenously-seeded infection may cause almost one third of all PJI cases [1]. In patients with joint prostheses in place, dental procedures have historically been considered a concern for producing a transient bacteremia that could potentially cause a hematogenously-seeded PJI [2,3]. Contributing to this concern are case reports in the literature that have attempted to link PJI temporally to dental procedures [4–12]. Such infections generally involve anaerobic organisms that could be expected to be part of the normal dental flora.

Given these concerns for possible hematogenous PJI from an oral source, questions have arisen regarding the value of antibiotic prophylaxis in joint arthroplasty patients undergoing dental procedures [13]. Both the American Academy of Orthopaedic Surgeons (AAOS) and the American Dental Association (ADA) have published guidelines with regard to such prophylaxis. The most recent of these, co-developed by the AAOS and the ADA, were issued in 2012 [14,15]. However, this latest guideline makes no definitive statement for or against antibiotic prophylaxis in arthroplasty patients prior to dental procedures. Overall recommendations indicate that there is limited evidence to support the practice of routine antibiotic prophylaxis for all dental patients with prosthetic implants and inconclusive evidence for or against the use of topical oral antimicrobials in these cases. There is a strong recommendation (unanimous consensus) for continued adequate oral hygiene in total joint replacement patients. More recently in 2016, the AAOS and ADA co-issued Appropriate Use Criteria for this topic [16]. The recommended actions seem to advocate an individualized approach for patients based upon the planned dental procedure, the immunocompromised status of the patient and the glycemic control of the patient, if the patient is diabetic. It can be argued that much of the conclusions of this latest report amount to nothing more than expert opinion/consensus.

A systematic review of the literature in this area yielded 90 individual studies, of which 9 [10,11,17–23] were felt to be adequate for inclusion. Six studies corresponded to a grade IV level of evidence, two studies to level III, and one study to level I. Methodological quality measurements showed an overall low quality of the included studies scoring a median of 6 (range 4 to 7) for case series studies [10,11,17–20]. The methodological quality of Berbari et al. [21], Skaar et al. [22] and Kao et al. [23] showed great heterogeneity in terms of study design and outcome assessment and mostly low methodological quality. Three of the studies were prospective in nature and the remaining were retrospective, six of them being

case-series, two case-controlled and only one retrospective cohort study. All were conducted between 1980 and 2016, 7 were conducted among patients treated at a single institution, and 2 included data collected from research databases (Taiwan National Registry [23] and Medicare Registry [22]). None of the studies have suggested and/or been indicated to postpone having an invasive dental procedure after a TJA.

Accordingly, there is still limited evidence to stand for or against the use of antibiotic prophylaxis prior to a dental procedure in joint arthroplasty patients. Although some retrospective articles have associated extensive dental procedures with PJI [10,11] a prospective case-control study found that neither low-risk nor high-risk dental procedures were associated with PJI [21]. In that study, Berbari et.al., studied dental prophylaxis prospectively in 339 PJI patients with 339 control patients. They found that antibiotic prophylaxis prior to a surgical procedure conferred no benefit in terms of reducing the incidence of PJI. However, the authors admit that the numbers studied might not have been enough to detect a minor increase in PJI following dental procedures [21].

The issue of whether undergoing a dental procedure soon after TJA increases the risk of implant seeding and potential PJI has not been studied. To design a study that would examine this issue would be challenging. We speculate that the seeding of an implant is more likely to occur if the impant has not osseointegrated. Thus, in patients undergoing uncemented TJA, delaying the invasive non-urgent dental procedures may minimize the risk of seeding without exposing the patient to any risk.

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QUESTION 3: What is the role of prophylactic antibiotics for invasive procedures (dental, gastrointestinal (GI), urologic, etc.) in the presence of an arthroplasty to prevent subsequent periprosthetic joint infection (PJI)?

RECOMMENDATION: There is no role for routine prophylactic antibiotic administration prior to dental or genitourinary (GU) procedures. There is limited evidence that has shown certain GI procedures may be associated with a risk of subsequent PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 64%, Disagree: 28%, Abstain: 8% (Super Majority, Weak Consensus)

RATIONALE

Dental Procedures

Transient bacteremia has been shown to occur following dental procedures [1,2]. There is a theoretical risk of hematogenous seeding of the prosthetic joint following transient bacteremia, however this is not necessarily borne out in the literature [3,4]. Further, there are two studies that show no difference in the rate of PJI between those patients who received antibiotic prophylaxis and those that did not. In a prospective case-control study of 339 patients, Berbari et al. showed that there was no statistically significant reduction in the rates of PJI in patients who received antibiotics prophylaxis [5]. In a large retrospective cohort study, Kao et al. identified 57,066 patients who had undergone dental treatment following total joint arthroplasty (TJA) and matched this cohort to patients who had undergone TJA and had not undergone dental procedures. The authors found no significant difference in the rate of PJI between the two group and, further, there was no difference in the rate of PJI for those who received antibiotics prophylaxis and those who did not [6]. With this evidence in mind, there is currently no evidence for routine antibiotic use for prophylaxis against PJI in patients undergoing dental procedures.

Genitourinary Procedures

GU procedures (including but not limited to) transurethral resection of the prostate (TURP), cystoscopy, urethral dilation, ureteral stenting and transrectal prostatic biopsy, have been shown to be associated with transient bacteremia [7–13] and there is a theoretical risk of seeding of the prosthetic joint via hematogenous spread. The literature regarding the subsequent development of PJI following GU procedures is limited. A number of case reports have documented PJI following TURP [14][15]. In a prospective, case-controlled study, Gupta et al. showed that there was no increased risk of PJI for patients undergoing GU procedures. They also noted that prophylactic antibiotics did not lower the rate of PJI, although it should be noted that a low percentage of patients in both the case and control groups received prophylactic antibiotics (1% and 2%, respectively) [16].

Gastrointestinal Procedures

GI procedures such as gastrointestinal endoscopy, colonoscopy and signmoidoscopy have been shown to produce transient bacteremia [17–19], most commonly in patients who are in an immunocompromised state [20,21]. There are several small-scale studies and case reports that have shown an association with PJI in patients following invasive gastrointestinal procedures [22–25]. Currently, there is only one single-center, case-control study which showed that esophago-gastro-dueodenoscopy with biopsy increased the risk of developing PJI (odds ratio (OR): 4, 95% confidence interval (CI) 1.5 to 10) [26]. While prophylactic antibiotics may be warranted in this situation and in high-risk patients, further investigation is needed to determine whether prophylactic antibiotics are necessary in all patients undergoing invasive gastrointestinal procedures, and whether their usage will successfully decrease the risk of PJI.

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QUESTION 4: Does the type of venous thromboembolic (VTE) prophylaxis influence the risk of surgical site infection/periprosthetic joint infection (SSI/PJI) in patients undergoing orthopaedic procedures?

RECOMMENDATION: Yes. In a majority of studies evaluating VTE prophylaxis in patients undergoing total joint arthroplasty (TJA), aspirin appears to result in a lower risk of SSI/PJI than anticoagulants (vitamin K antagonists, heparin-based products, factor Xa inhibitors and direct thrombin inhibitors).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 80%, Disagree: 10%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

The risks versus benefits of VTE prophylactic agents in patients undergoing orthopaedic procedures, particularly TJA, remain controversial. Current Academy College of Chest Physicians (ACCP) guidelines recommend agreement with American Academy of Orthopaedic Surgeons (AAOS) guidelines for VTE prophylaxis and recommend pharmacologic prophylaxis over no prophylaxis, but do not provide support for or against any specific pharmacologic agent [1]. The most recent 2012 ACCP guidelines also recommend pharmacologic prophylaxis in all patients without a high risk of bleeding, but do not specify an agent [2,3]. Current commonly-used pharmacologic agents for prophylaxis following TJA include aspirin, vitamin K antagonists (i.e., warfarin), heparin-based anticoagulants (including low molecular weight heparins (LMWH), i.e., enoxaparin or dalteparin), direct oral anticoagulants (DOACs, i.e., rivaroxaban or apixaban) and direct thrombin inhibitors (DTIs, ie., dabigatran) [4].

Wound drainage, bleeding and hematoma formation have been associated with PJI [5,6]. Therefore, balance of thrombotic risk and bleeding risk becomes paramount in selection of the appropriate postoperative VTE prophylaxis.

A literature review was performed using the PubMed and Cochrane Database of Systematic Reviews. The Medical Subject Headings (MeSH) terms "venous thromboembolism," "prophylaxis," "arthroplasty" and "infection" were searched. Studies were identified to be related to VTE and arthroplasty based on their title and abstract. They were then reviewed and included if a reported outcome measure was PJI or SSI.

Low Molecular Weight Heparin

The 2012 ACCP guidelines suggest the use of LMWH for postoperative VTE prophylaxis due to extensive data supporting its efficacy and safety in medical literature [7]. However, there is conflicting evidence in the orthopaedic literature regarding the rate of complications with its use following TJA. Multiple studies in recent orthopaedic literature suggest that LMWH after TJA may result in increased SSI/PJI and wound complications. Kulshrestha et al. [8] randomized patients undergoing primary total knee arthroplasty (TKA) to receive routine LMWH prophylaxis or risk stratification with the American Society of Anaesthesiologists (ASA) physical status score for standard risk and selective use of LMWH in high risk patients. They found that patients on LMWH had almost eight times the risk of wound complications compared with patients receiving ASA. Patel et al. [6] found that LMWH, compared with ASA and warfarin, was an independent risk factor for prolonged wound drainage following primary TJA. A prospective cohort study from the Global Orthopaedic Registry (GLORY) showed a significantly higher rate of SSIs in 1,561 patients receiving LMWH prophylaxis dosing (1.6% SSI) compared with 2,194 patients receiving therapeutic warfarin with or without bridging therapy (0.6% SSI) [9]. Burnett et al. [10] studied 290 patients undergoing TJA that received LMWH for 10 days postoperatively (3.4% required return to OR for wound complications). However, multiple other studies, including the RECORD 1-4 randomized control trials (RCTs) found no difference in SSI/PJI rates in patients undergoing TJA receiving either rivaroxaban or enoxaparin [11–14].

Factor Xa Inhibitors

There is conflicting evidence in current literature regarding rates of SSI and PJI in TJA patients receiving factor Xa inhibitors compared to other pharmacologic prophylaxis. Two recent meta-analyses of RCTs found no difference in SSI/PJI rates in TJA patients receiving rivaroxaban versus enoxaparin [11,15]. Multiple other retrospective studies have also found similar rates of PJI and superficial wound infections in patients receiving rivaroxaban and enoxaparin [7,16,17]. Agaba et al. [18] performed a retrospective review of 25,966 patients undergoing total hip arthroplasty (THA) receiving a single medication for VTE prophylaxis from the Humana National Healthcare Database between 2007 and 2016. 2.12% of patients received ASA, 26.15% enoxaparin, 46.25% warfarin, 1.3% apixaban, 3.37 fondaparinux and 20.81% rivaroxaban. They found that rivaroxaban had the lowest risk of PJI [18]. However, multiple studies have also found an increased risk of early SSI requiring reoperation following TJA with use of rivaroxaban compared to enoxaparin [19,20].

Direct Thrombin Inhibitors

Evidence regarding direct thrombin inhibitors is also unclear. Multiple studies have found that the use of dabigatran following TJA leads to prolonged wound drainage and increased risk of SSI/PJI. Gill et al. [21] found a 7% rate of reoperation for wound infection with dabigatran prophylaxis following TJA compared to 1% with a protocol of dalteparin while inpatient and ASA after discharge. Aquilina et al. [22] prospectively studied a cohort of 110 patients undergoing TJA and found mean of 6.6 days of wound drainage with dabigatran versus 3.4 days with ASA. Other studies have also found longer periods of wound drainage in patients receiving dabigatran prophylaxis compared with apixaban, enoxaparin and aspirin [23,24]. Bloch et al. [24] found a 20% wound drainage rate in TJA patients following introduction of use of dabigatran prophylaxis compared to 5% when using a multimodal regimen of LMWH while inpatient and ASA as outpatient. However, the RE-NOVATE (Clinical trial examining:

"dabigatran etexilate compared with enoxaparin in prevention of VTE following THA") and RE-NOVATE 2 RCTs compare dabigatran with enoxaparin for prophylaxis following THA and found no difference in wound infection rates [25].

Warfarin

Many recent studies have shown that SSI/PJI rates in TJA patients receiving warfarin prophylaxis are significantly higher than those receiving ASA prophylaxis. Sachs et al. [26] studied 785 patients treated without any pharmacologic prophylaxis compared with 957 patients treated with warfarin postoperatively and found similar VTE rates, but twice the infection rate in the warfarin group (0.6% vs.0.3%). Huang et al. [27] performed a single institution retrospective cohort study with 25,372 TJA patients receiving warfarin titrated to an international normalized ratio (INR) of 1.8 to 2.0 versus 4,898 TJA patients receiving ASA and found a 90-day postoperative PJI rate of 1.28% in the warfarin group compared to 0.22% in the ASA group. Other studies have also found prolonged wound drainage and significantly elevated PJI rates with warfarin compared with ASA following primary TJA [28–30]. However, Deirmengian et al. [31] found no difference in 90-day SSI rates in revision TJA patients receiving ASA versus warfarin, but found that ASA was more effective for VTE prevention. Comparing warfarin to other pharmacologic anticoagulation, evidence is less clear. As discussed above, Wang et al. [9] studied patients undergoing primary TJA from the Global Orthopaedic Registry and found significantly lower rates of superficial and deep infection in patients receiving warfarin prophylaxis compared with enoxaparin. Cafri et al. [32] found no significant difference in 90-day postoperative SSI rates between groups receiving ASA 325 mg once daily, fondaparinux 2.5 mg daily, LMWH 30 mg twice daily (BID) or 40 mg daily, and warfarin (goal INR 1.5 to 3.0) in a cohort of 30,499 patients from the Kaiser Permanente Total Joint Replacement Registry.

Aspirin

As discussed above, many studies have demonstrated lower SSI/PJI rates with ASA prophylaxis compared with warfarin prophylaxis. Other studies also demonstrate lower rates of infection and wound problems with ASA versus other anticoagulants. Kulshrestha et al. [8] randomized 450 TKA cases to either routine anticoagulation with 40 mg daily enoxaparin and 450 TKA cases to risk stratification and aspirin in low risk patients or enoxaparin in elevated risk patients. In patients receiving enoxaparin, there was nearly eight times the number of wound complications. Garfinkel et al. [33] found significantly higher rates of bleeding and wound complications with rivaroxaban compared with ASA.

Conclusion

The effects of specific anticoagulants on postoperative SSI and PJI remain uncertain. Rates of SSI/PJI with aspirin prophylaxis appear to be lower than rates with anticoagulation. Nevertheless, there is little level I evidence to support differences in risk of SSI/PJI between modes of pharmacologic VTE prophylaxis. Although many RCTs have been performed to evaluate the efficacy of various pharmacologic agents in prevention of VTE and their effects on other major complications such as bleeding and death, few report on the incidence of SSI and PJI in their treatment groups. Additionally, the definitions of SSI and PJI are heterogeneous across studies, making it difficult to compare infection rates. Finally, various dosages of the different pharmacologic agents need to be studied to determine their effect on SSI/PJI rates.

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1.20. PREVENTION: HOSPITAL ENVIRONMENT

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QUESTION 1: Does prolonged hospitalization prior to elective total joint arthroplasty (TJA) increase the risk of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Yes. Prolonged preoperative hospitalization is associated with an increase in the risk of SSI/PJI.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 96%, Disagree: 3%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Previous studies from various surgical disciplines have demonstrated an increased risk of SSI secondary to prolonged preoperative hospitalization [1–7]. These findings may be confounded by medical comorbidities known to increase the risk of SSI that require optimization in an inpatient setting prior to surgical intervention [5]. Considering this, it must also be acknowledged that there is a risk of exposure to and colonization of pathogenic microorganisms in healthcare settings [6,8].

Quantitatively, there is no consensus on the definition of prolonged hospitalization prior to elective TJA. Studies have reported this as same-day and on-same-day surgery [9–11], days prior to surgery (more than two days, three days, more than three days or more than four days), median preoperative waiting time, or with no exact time period [1,12–17]. Despite this, all of them agree there is a positive correlation between length of preoperative stay and the increased risk of SSI or PJI.

A case-control study by Lee et al. reviwing the risk factors for SSI amongst elderly orthopaedic patients found that admission on the day of surgery was associated with a decreased risk for SSI (odds ratio (OR): 0.42, 95% confidence interval (CI) 0.24 to 0.74, p = 0.002) in a bivariate analysis [9]. A multivariate analysis conducted of the same study group found that the only independent predictor of SSI was admission from a healthcare facility (a nursing home, rehabilitation facility or another hospital) (OR: 4.35, 95% CI 1.64 to 11.11, p = 0.003) [9]. Furthermore, in a series study of 3,672 primary hip arthroplasty cases, Maoz et al. reported non-same-day surgery as a significant risk factor for PJI (OR: 4.16, 95% CI 1.44 to 12.02, p = 0.008) [10] following multivariate analysis. Utilizing studies looking at infection in spinal surgery as a comparison, the infected cases had a longer length of stay preoperatively compared to non-infected cases (mean 2.4 vs.0.9 days, p = 0.002) [12]. The risk of SSI/PJI increases for total hip and knee arthroplasty patients with a preoperative stay greater than three days (OR: 1.81, 95% CI 1.15 to 2.84, p = 0.03) [4,13,15].

It is recommended that preoperative hospitalization be kept as short as possible in an effort to reduce the risk of SSI/PJI [7,18,19], It is suggested that patient admission for an elective procedure such as total hip arthroplasty be avoided prior to the day of surgery [11] given that a longer delay to operation is an independently significant risk factor for SSI [20].

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QUESTION 2: Does placement of patients with an infection in private hospital rooms decrease the risk of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI) for patients undergoing orthopaedic procedures?

RECOMMENDATION: There is some evidence to suggest that isolation of patients who are carriers of or are infected with methicillin-resistant *Staphylococcus aureus* (MRSA) in private rooms, as well as observing isolation protocols, reduces the rate of hospital-acquired infections. Patient isolation and contact precaution measures also play a key role in controlling outbreaks due to other multi-drug resistant organisms such as vancomycin-resistant enterococci (VRE), *E. coli*, *Klebsiella*, *Acinetobacter*, *Pseudomonas* and others. The issue of whether placing orthopaedic patients with an active infection in private rooms has any effect on the rate of PJI for other patients has not been examined.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 88%, Disagree: 5%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

SSIs are a disastrous complication in orthopaedic surgery, which overburden the healthcare systems by adding to patient morbidity, mortality and cost of treatment. Approximately 50% of SSIs can be prevented by following evidence-based strategies recommended for their prevention [1]. *Staphylococcus aureus* is the most common organism isolated in orthopaedic SSI, accounting for approximately 30 to 40% of the cases in various series [2–4]. More importantly, the rising incidence of MRSA, which is reported to be present in 10 to 35% among orthopaedic SSIs in some series, is a matter of concern [2,5,6]. Multiple strategies have been recommended for prevention of SSIs including surgical hand preparation, surgical site preparation, perioperative antibiotic prophylaxis and multi-modal interventions for certain highly-resistant organisms, especially MRSA [7,8]. These multi-modal interventions, also called "bundles," include preoperative screening of patients, isolation of carriers, contact precautions, decolonization and the judicial use of antibiotics. Bundles have been proven to be very effective in reducing rates of transmission from carriers and SSI caused by resistant organisms, especially MRSA [9], and prevention of outbreaks of other multi-drug resistant organisms (MDROs) such as VRE and extended spectrum beta lactamase (ESBL) producing organisms like *E. Coli*, *Klebsiella*, *Acenitobacter,* etc. [10]. In a study conducted over a period of 18 months involving multi-specialty surgical units of a Swiss teaching hospital, implementation of such infection control measures for MRSA led to extremely low levels of overall nosocomial MRSA infection rate at 0.77% (169 out of 21,754) [11].

Transmission of infection in a hospital occurs from patient to patient, through transiently-colonized healthcare workers, contact with contaminated surfaces and airborne dispersal. Isolation measures are fundamental to interrupt this transmission. The role of isolation of patients with active infection and those who are carriers for highly-resistant organisms in private rooms and its effect on the risk of subsequent SSI/PJI has been discussed in this review.

At the outset, it is important to understand whether colonization with these high-risk organisms increases the chances of subsequent SSI/PJIs. Several studies [12–14] have concluded that colonization with *S. aureus* and MRSA is an important risk factor for SSIs following orthopaedic surgeries. In a recent study involving 4,148 patients who underwent orthopaedic surgical interventions, Nakamura et al. [2] found that patients with nasal carriage of *S. aureus* had a significantly higher incidence of SSI (1.16%) as compared to non-carriers (0.39%). In a systematic review by Levy et al. [14] including five studies, they established that nasal carriage of *S. aureus* (including MRSA) is a major risk factor for orthopaedic SSIs. While this is true for infection with *S. aureus* and MRSA, a cause-effect relationship for SSI has not been established for colonization by other MDROs. This may be explained by the fact that the colonizing strains of these later organisms and those causing outbreak differ in their pathogenicity in causing SSIs and other hospital-acquired infections (HAIs) [15].

The second aspect is to determine the effectiveness of patient isolation in single rooms in reducing the risk of subsequent SSI/PJI. Since isolation strategies concomitantly include implementation of screening/surveillance techniques with or without decolonization, along with hand hygiene and contact precautions (such as use of separate gowns, gloves, etc.), it is difficult to determine the singular role of isolation separately.

We conducted a comprehensive literature search for studies evaluating the role of isolation of infected/colonized patients and the rates of SSI in patients undergoing orthopaedic surgeries. Most of these studies were pertaining to MRSA and involved multiple interventions (including surveillance, contact isolation, decolonization and antibiotic prophylaxis) for MRSA control. Out of 24 studies reviewed, 15 evaluating the efficacy of *S. aureus*/MRSA screening and decolonization were excluded because "patient isolation" was not specifically performed or mentioned. After reading the selected articles, nine studies [9,16–23] were chosen for this review, all of which provided conclusive evidence that multi-modal interventions were effective in decreasing SSI caused by MRSA. Analysis of combined data from these studies showed that MRSA control measures (including isolation) led to reduction in the rate of SSI from 1.14% (199 out of 17,457) to 0.38% (128 out of 33,328). In another prospective interventional study by Sankar et al. [24], patients undergoing hip or knee arthroplasty were subjected to pre-admission MRSA screening. Positive patients received topical decolonization therapy and their admission was postponed until three consecutive swabs from three body sites were negative. After application of this protocol, they found a significant reduction in the overall incidence of healthcare-associated infections (HAIs) (from 8.5% to 3.5%) and mean length of hospital stay (from 10.43 days to 9.47 days).

In the latest World Health Organization (WHO) guidelines for prevention of SSI, it has strongly recommended that patients undergoing orthopaedic surgery who are nasal carriers of *S. aureus* should be decolonized with intranasal mupirocin 2% ointment, with or without chlorhexidine gluconate body wash [7]. Similarly, in a systematic review of preventive measures for healthcare-associated infections by MRSA, Kock et al. [25] concluded that mupirocin-based decolonization therapy should be considered for *S. aureus* carriers who are undergoing orthopaedic surgery.

To achieve optimal impact, these isolation measures should be implemented along with hand hygiene, education of healthcare workers and rational use of antibiotics. In fact, in a prospective study by Spence at al. [26] where all patients were housed in single rooms and good hand hygiene practices were followed, it was found that following additional "contact precautions" for asymptomatic MRSA carriers had no effect on rate of hospital-acquired MRSA infections and was relatively expensive.

Many countries have introduced strict guidelines as part of nationwide policies in order to reduce the rates of HAIs, especially those caused by resistant organisms such as MRSA. The "search and destroy" policy, which has been implemented in countries like the Netherlands, Belgium, Germany and Sweden to control and maintain low endemic levels of MRSA, includes screening of patients on admission for MRSA, contact isolation of MRSA-positive patients in single rooms, pre-emptive isolation and screening of high-risk patients, decolonization and follow-up screening, healthcare worker screening and suspension from work until decontamination is achieved [27]. Likewise, implementation of a "search and isolate" strategy in a region hyper-endemic for MRSA has been reported to cause significant reduction in MRSA bacteremia from 0.64 to 0.30 per 1,000 admissions [28].

Active surveillance cultures (ASC), which involves the universal screening of all patients whether or not they exhibit signs or symptoms of infection in order to detect infected as well as colonized patients, have proven to be effective in controlling the spread of MRSA and VRE [29]. However, the Association for Professionals in Infection Control and Epidemiology (APIC) and Society for Healthcare Epidemiology of America (SHEA) do not support legislative mandates for use of ASC [30]. "Targeted surveillance" based on patients' risk factors is almost equally as effective and more cost-efficient as compared to universal screening [31]. Various risk factors for MRSA colonization include previous hospitalization or surgery, previous therapy with quinolones or cephalosporins, advanced age, dialysis, underlying chronic illness, residency in long-term-care facility, eczema or psoriasis, history of promiscuity or prison, pressure sores and intravenous drug abuse [32].

Although adequate literature has been published on MRSA, very few studies have evaluated the role of isolating patients infected with other MDROs like VRE, ESBLs (*E. coli* and *Klebsiella*), multi-drug resistant *Acenitobacter* and *Pseudomonas*, etc. in preventing SSI. These organisms become increasingly significant in the intensive care unit (ICU) setting rather than the ward setting. Contact precautions and patient isolation have proven to be the cornerstones of the control measures to be undertaken during an outbreak [33], but the role of routine isolation of patients who are carriers of these MDROs in preventing SSIs and other HAIs is unknown. It has been suggested that the outbreak strains of these MDROs may be different from the colonising strains in terms of transmissibility and capacity to survive on epithelial surfaces [15]. *Acenitobacter* species is an increasingly important source of nosocomial infection in recent years accounting for up to 20% of SSIs following orthopaedic surgeries [3] and is capable of causing other HAIs such as pneumonia, meningitis and bacteremia [34]. Gogou et al. [35] reported an outbreak of MDR (carbapenem-resistant) *Acenitobacter baumanii* in the orthopaedic ward with 29 cases reported within 2 years despite strict control measures, eventually requiring relocation of the department. The ability of the organism to contaminate and survive in the environment such as traction table, wash basins, suction drains, catheters, etc. has been highlighted in the study as causing difficulty in eradication. Such reports serve as a reminder for implementation of immediate control measures on identification of such MDROs. As per the guidelines of the US Healthcare Infection Control Practices Advisory Committee, full contact precautions (including admission to a single patient room, wearing a gown and gloves for all interactions involving contact with patient and discarding them before exiting the patient room) should be followed to prevent the transmission of these MDROs during outbreaks [10]. Avoidance of overcrowding and understaffing and routine environmental cleaning has shown to reduce transmission of MDROs [36–38]. While isolation strategies appear to have a definite role in preventing the outbreak of these organisms, the effect of their routine application on reducing orthopaedic SSI/PJI is not clearly defined.

In a recent study involving 2,255 arthroplasty patients, Navalkele et al. [39] concluded that recent respiratory tract infections (within 30 days prior to surgery) increased the risk of SSI. In another systematic review and meta-analysis of risk factors for PJI, Zhu et al. [40] found no significant association between urinary tract infection (UTI) and risk of PJI. Although the role of contact isolation in cases of infections other than those caused by MDROs such as UTI, respiratory tract infections, skin infections etc. has not been studied, it is a general protocol at many centers to keep such patients isolated from other patients undergoing elective orthopaedic procedures.

Another strategy that has given beneficial results by advocating isolation of patients is the concept of a "ring-fenced" orthopaedic center. This has been followed in the United Kingdom (UK), and involves the creation of separate wards where only patients undergoing clean, elective orthopaedic surgeries are admitted. It excludes

admission of patients with known or suspected infection, patients colonized with MDROs, patients with chronic wounds or abscess, patients with active chest infection, patients undergoing bowel surgery and patients with long-term indwelling devices who are requiring antibiotic treatment at the time of admission. We found three studies (two prospective and one combined prospective and retrospective) in which ring-fencing of elective orthopaedic wards was implemented [21–23]. Combined analysis of data from these 3 studies show that ring-fencing was effective in decreasing the rate of SSI from 1.31% (57 out of 4,347) to 0.35% (32 out of 9,230). In a study in the UK, Barlow et al. [21] found that creation of a dedicated arthroplasty ward resulted in a decrease in the incidence of SSI and reduction in mean length of hospital stay amongst patients undergoing primary lower limb arthroplasty.

Although placement of patients in single rooms provides infection control benefits, it has not been proven by studies conducted either in the ICU setting or outbreak situation [41–45]. In a review article by van de Glind et al. [46], the authors could not find an association between single patient rooms and reduced infection rates. Various studies have cited negative effects of isolation including anxiety, depression and negative impacts on patient care, safety and satisfaction [47–49]. However, in a recent prospective survey by Chittick et al. [50], the majority of patients in contact isolation were happy with the privacy, felt safe and were satisfied with the quality of care. Adequate education of patient and care-giver at the time of isolation plays an important role in minimizing these adverse effects.

In a systematic review analyzing the cost-benefit of infection control interventions targeting MRSA, Farbman et al. [51] found a median save/cost ratio of 7.16 with 15 out of 18 studies showing a favorable cost/benefit ratio. Higher benefits were observed in intermediate to highly-endemic settings.

Due to lack of well-designed studies which precisely define the exclusive role of isolation of infected patients in preventing surgical site infection and heterogeneity of data in the available studies, a systematic meta-analysis on this question was not possible. Nonetheless, there is definitive evidence of the beneficial role of isolation (along with other interventions) in preventing MRSA SSI.

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Diagnosis

2.1. DIAGNOSIS: DEFINITIONS

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QUESTION 1: What is the recommended time interval that would divide acute and chronic periprosthetic joint infection (PJI) (4 weeks, 90 days, etc.)?

RECOMMENDATION #1: There is no evidence-based time interval that divides acute from chronic PJI. The natural history of infection is a continuum from initiation to chronicity. Surgical treatment for patients with infection should not solely be based on the duration of symptoms or the time from implantation of the prosthesis. Other factors should also be considered such as implant stability, presence of sinus tract, virulence of the infective organism and the general health of the patient. It is important to note that the efficacy of surgical intervention, involving retention of the prosthesis, is more likely to fail as one moves past four weeks from the index arthroplasty and/or duration of symptoms of infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 84%, Disagree: 15%, Abstain: 1% (Super Majority, Strong Consensus)

RECOMMENDATION #2: We recommend moving away from the traditional division between acute and chronic infection based solely on time from index arthroplasty or duration of symptoms. Periprosthetic infection is a continuum that leads to establishment of biofilm.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 60%, Disagree: 34%, Abstain: 6% (Super Majority, Weak Consensus)

RECOMMENDATION #3: Should we have a specific time limit cutoff between chronic and acute infection?

DELEGATE VOTE: Agree: 60%, Disagree: 37%, Abstain: 3% (Super Majority, Weak Consensus)

RATIONALE

According to the *Oxford Advanced Learner's Dictionary*, the term "acute" in the case of illness is defined as "coming quickly to the most severe or critical stage" and the term "chronic" as "lasting for a long time, happening continually." In the case of an acute PJI, this would be translated as a sudden onset of severe joint pain and/or swelling in a priorly symptom-free prosthetic joint, and in case of chronicity, as the presence of mild or moderate pain in which its exact onset is hard to establish. In our opinion, this is the most accurate definition to differentiate acute from chronic PJIs, and reflects the virulence of the microorganism(s) causing the infection. The reason that a certain time frame was subsequently introduced in the world of PJI to divide acute from chronic infections was primarily based on clinical grounds to identify those patients with a high and low success rate when treated with debridement, antibiotics and retention of the implant (DAIR) [1–15].

One of the factors associated with DAIR failure is the presence of a mature biofilm in which embedded bacteria are unresponsive to antibiotic treatment due to multiple phenotypic and genotypic changes [16,17]. In such a condition, a PJI cannot be cured with antibiotics alone without removal of the implant. In which time frame a biofilm reaches maturity is not clear. In vitro studies indicate that biofilm start to form within just hours after inoculation of bacteria [18], but these experiments are performed under "optimal" circumstances for bacterial growth and do not include the complexity of the host's environment and the protective effect of its immune system [19]. Carli et al. observed in a mouse model with a proximal tibial implant infection, using a high initial bacterial inoculum ($3x10^5$ CFU) that a biofilm is evident after two weeks of injection, but extends and is covered by fibrinous tissue and multiple host cells after six weeks [20]. A recent mouse model of knee PJI using a low infecting inoculum of *S. aureus* (10^3 CFU) (which is similar to the expected inoculum during surgery [21]) demonstrated that after a two-weeks incubation period, antibiotic combinations including rifampin were able to eradicate the infection [22]. These studies suggest that a mature biofilm develops within two to six weeks. However, the process of biofilm formation varies greatly among bacterial species, its inoculum and the host [23,24]. Accordingly, it has been demonstrated that the efficacy of DAIR in acute infections is highest when the DAIR is performed as soon as possible after the onset of symptoms [25–36]. Moreover, it is important to note that, since the success of DAIR is determined by many factors, the decision to perform a DAIR procedure should not solely be based on symptom duration and/or time from index surgery in acute PJIs, but should include host related factors, causative microorganism and the stability of the implant. For this reason, we propose not to include a time interval in the definition of acute and chronic PJI since the natural history of an infection is a continuum from initiation to chronicity.

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QUESTION 2: What is the definition of implant "colonization" vs. implant-related infection?

RECOMMENDATION: Colonization is the presence of microbiota in a joint with growth and multiplication of the organism, but without interaction between the organism and the host's immune response thus avoiding any clinical expression. Infection is the invasion of a joint by disease-causing organisms that results in an interplay with the host's immune response, causing a clinical expression and disease state.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 83%, Disagree: 8%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

Over the last few years, extensive research efforts have been invested in the diagnosis of implant-related infection or periprosthetic joint infection (PJI) and numerous definitions have been proposed [1–3]. Infections result in an immune response, thus all definitions rely on a combination of clinical findings, laboratory results from peripheral blood and synovial fluid, microbiological data, histological evaluation of periprosthetic tissue and intraoperative findings. The advancements in the field of diagnostics and statistics have allowed us to establish a validated, evidence-based definition for PJI as presented in another section.

On the other hand, research into colonization of a prosthetic joint implant is scarce and currently there is no universally-accepted

definition for implant colonization. Colonization and infection are two different processes. There are approximately 10 times as many bacterial cells in the human flora as there are human cells in the body, thus all multicellular organisms are colonized to some degree by extrinsic organisms. The human microbiome is the collection of all the microorganisms living in association with the human body. Microbiome and host form a complex relationship, where microorganisms can confer symbiotic benefits to the host in many key aspects of life [4]. However, defects in the regulatory circuits of the host-microbiome interaction may disturb this symbiotic relationship and promote disease [5]. The difference between an infection and colonization is often only a matter of circumstance. Non-pathogenic organisms can become pathogenic given specific conditions, and even the most virulent organism requires certain circumstances to cause a compromising infection.

Analysis using next-generation sequencing (NGS) has improved understanding of the microbiome [6,7]. Recent studies suggest the presence of microbiome in aseptic deep tissue [7–9]. This is a fascinating discovery, as it suggests that microorganisms may inhabit organs previously thought to be sterile, given that they do not communicate with the outside world. In a recent study using NGS, an organism was identified in 6 of 17 patients undergoing primary arthroplasty, with no clinical or laboratory evidence of infection [10]. In another recent study NGS frequently identified multiple organisms in an infected sample and the question remains whether these infections are the result of a single dominant organism or multiple pathogenic organisms [11]. This becomes of particular concern when considering that the majority of patients who fail treatment for infection are infected with a different organism [12,13].

As we forge new alliances in our quest to eliminate prosthetic joint infections, we should also consider a call to new and mutually-beneficial ways of coexisting with the microbial flora of the world. Novel molecular techniques for organism detection provide comprehensive information on the organisms occupying the joint and thus hold the promise for a better understanding of joint colonization.

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QUESTION 3: What is the definition of a sinus tract?

RECOMMENDATION: A sinus tract has the following characteristics: (1) it is an abnormal channel through the soft tissues that allows communication between a joint prosthesis and the outside environment, known or presumed to be colonized by bacteria and (2) its presence may be confirmed with direct visualization of an underlying prosthesis, evidence of communication with fistulogram, ultrasound, computed tomography (CT) or magnetic resonance imaging (MRI).

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 97%, Disagree: 2%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

The presence of a sinus tract communicating with a total joint arthroplasty (TJA) is one of the two major criteria for the diagnosis of periprosthetic joint infection (PJI) proposed by the Musculoskeletal Infection Society (MSIS) and the International Consensus Meeting [1]. Therefore, consistently defining what constitutes a sinus tract in this context has significant implications for the appropriate diagnosis and treatment of PJI. Interestingly, there is a paucity of information in the arthroplasty literature that defines the characteristics of a periprosthetic sinus tract. Many investigations discuss the presence and subsequent surgical management of sinus tracts in the setting of knee and hip arthroplasty but do not provide consistent or detailed descriptions of the cutaneous pathology. Given the lack of information and evidence, it is important to develop a comprehensive and standardized method for characterizing a soft tissue sinus tract surrounding a total joint prosthesis.

A sinus tract (latin: hollow, cavity) is an abnormal channel connecting a cavity lined with granulation tissue to an epithelial surface [2]. Although a fistula and a sinus tract are technically separate entities, with the former representing an abnormal connecting

channel between two epithelialized cavities specifically, [2] they are frequently grouped together.

Given the relationship between infection and the development of sinus tracts and vice versa, it is not surprising that there exists a rich accounting of draining wounds and sinus tracts throughout medical history. In fact, a likely description of a draining sinus tract, secondary to chronic shoulder infection and osteomyelitis, is included in the Edwin-Smith Papyrus [3], the oldest surgical treatise in existence. Centuries later, Hippocrates [4] would provide various descriptions of sinus tracts and fistulae and extensive options for remedies, including topical, oral and surgical.

However, perhaps the most important of the historical treatments of sinus tracts comes from the 1686 *Chirurgical Treatises* of Richard Wiseman [5]. In his chapter titled "On Fistulae," which appears in the appendix to his treatise on gunshot wounds, Wiseman describes a fistula as a sinuous ulcer, which has actively been draining for at least two to three months. He associates the draining sinus fistula with a "long pipe of skin" and the presence of "callus" which has been "hastened by the transpiration and resolution of the thin and subtill humours." Like Hippocrates, Wiseman advocated for treatment with either medications or surgical debridement. Of note, Wiseman specifically commented upon the particular difficulty of curing sinus tracts associated with joints.

Since Wiseman, there have been numerous additional descriptions of sinus tracts associated with bones and joints. However, one of particular interest to the field of arthroplasty dates from the early 1700s [6]. Johanne Daniele Schlichting describes a case report from 1730 of a 14-year-old girl suffering from disability due to a hip infection associated with a large draining sinus tract. Schlichting also describes his method of treatment including removal of the femoral head and in doing so provided the first report of a proximal femoral resection in the medical literature. Throughout surgical history, a sinus tract has been pathognomonic for deep infection. The same is true in TJA, but the terms of the definition have not been established.

Sinus tracts are currently synonymous with PJI [7]. Fistulas in TJA have been noted to form connections between the prosthesis and vascular channels [8], the ureter [9], bladder [10,11], colon [12], rectum [13] and vagina [7], and are clearly a risk for the development of PJI when associated with bacterially-colonized cavities. Additionally, there is little information differentiating a communication that originates from inside the joint versus outside the joint.

There has been a significant amount of effort spent on determining the yield of culture samples from sinus tracts and fistulas originating from or terminating at joint arthroplasties [8,13–20]. Although this has provided insight as to the utility of sinus content cultures in the diagnosis of the responsible pathogens, it has not further assisted in defining the pathology. For the purposes of PJI diagnosis, we suggest that sinus tracts and fistulas communicating with bacterially-colonized areas should be grouped together, regardless of origin from within the joint or without, in order to fulfill the major criterion for the diagnosis of PJI.

The majority of information regarding the definition of a sinus tract in the presence of musculoskeletal infection has been studied in the context of osteomyelitis. There are multiple classification systems for sinus tracts, with varying degrees of focus on associated soft tissue compromise. The Cierny-Mader classification is perhaps the most commonly-referenced system, and involves categorical divisions staged by combining anatomic class (I: medullary, II: superficial, III: localized and IV: diffuse) and host physiologic class (A: normal immune function, B: local or systemic immune compromise and C: treatment worse than disease) [21]. A sinus tract leading to exposed bone is the hallmark of Stage II (superficial) osteomyelitis and occurs on a continuum with Stage III and IV disease. Although further details of sinus tract characteristics aside from direct contact with osseous structures are not included, treatment with thorough debridement is consistently advocated [21,22]. Conceptually similar to the anatomic class used by Cierny and Mader, Ger proposed a classification system in 1984 that focused on the wound, separating simple sinus, chronic superficial ulcer, multiple sinuses and multiple skin-lined sinuses [16]. Similarly, these pathologic conduits tunneled directly to bone. Currently, no analogous method is used to characterize sinus tracts associated with PJI. However, a patent channel through soft tissue connecting the outside environment directly to a total joint prosthesis should be considered a sinus tract.

Chronicity of drainage and of associated symptoms is an important consideration. Although it has been noted that postoperative wound drainage lasting longer than five to seven days is unlikely to remit without intervention [14], differentiating between simple prolonged postoperative drainage and early sinus tract formation is difficult. Galat et al. [15], reviewed the records of over 17,000 primary total knee arthroplasties and identified a 5.3% to 6.0% risk of deep infection in knees with persistent wound drainage within a 30-day postoperative time frame. However, "surgeon judgment" rather than objective testing played a significant role in the diagnosis of deep infection in many cases and may have skewed results. Another series of over 11,000 arthroplasty procedures identified 300 patients who developed wound drainage lasting > 48 hours following surgery [17]. Although persistent wound drainage was noted to cease in the majority of patients between postoperative days 2 to 4, 28% continued to drain and underwent further surgery. Surgical debridement was adequate to resolve the wound issues in the majority of cases but 20% required additional intervention in the form of two-stage exchange, resection arthroplasty or antibiotic suppression. In this series, the mean interval between the onset of drainage and surgical treatment was 10 days in patients who required further intervention.

Other studies have suggested that drainage of greater than 5 days imparts a 12.5-times risk of developing infection [23] and each day of continued drainage increases the risk of wound infection by 42% in hips and 29% in knees [24]. However, these studies do not subdivide the portion of superficial wound infections that progress to true PJI. In addition, surgery on a draining wound performed following 12 days of continuous drainage was noted to yield positive cultures in only 25% of cases [25]. While the distinction between persistent wound drainage and a developed sinus tract is not defined in the acute setting following surgery, there is likely a time after which persistent drainage should be deemed a sinus tract. Currently, there is no evidence to guide us, to our knowledge, in understanding this distinction. Regardless of the definition, persistent drainage in any form is clearly concerning for PJI.

There is a strong association between chronically-draining wound sinus tracts and deep infection of prosthetic hip and knee joints [26]. However, it is important to draw a distinction between the presence of a sinus tract *de facto* as a diagnostic criterion for PJI and the utility of sinus tract cultures in guiding infection treatment. Wound sinus cultures for osteomyelitis have notoriously low sensitivity and specificity [20,27,28]. The same has proven true for deep prosthetic joint infection. Two studies have been conducted to determine the correlation between superficial cultures from wounds or draining sinus tracts and a deep pathogen in the setting of prosthetic joint infection. Cune et al. evaluated the usefulness of wound culture results in the treatment of acute postoperative prosthetic joint infection. They found 80.3% agreement between superficial and deep surgical cultures in this setting with high sensitivity and specificity for *Staphylococcus aureus* and gram-negative bacilli [29]. Tetreault et al. performed a similar analysis comparing superficial and deep cultures in patients with deep prosthetic joint infection. Their results showed a 47.3% concordance between superficial and deep cultures, and in 41.8% of cases, the superficial organism

wound has guided therapy with a different antibiotic than deep cultures [30]. There is likely a gradient of organisms within a sinus tract community, but the biology of the sinus tract microenvironment has not yet been studied. Therefore, although the presence of a sinus tract should be considered equivalent to a deep prosthetic joint infection, cultures of the fluid cannot be relied upon to guide treatment.

In general, for the diagnosis of PJI, a sinus tract should demonstrate clear communication between the prosthesis and a non-sterile environment. The most obvious method is to directly visualize the underlying prosthesis through the lumen of the sinus or directly access the prosthesis with a sterile probe. However, to corroborate physical exam findings or evaluate a suspicious channel, various imaging methodologies may be utilized to confirm the presence of a true sinus tract that communicates with a TJA. Conventional radiography may be helpful in identifying areas concerning for infection with a sinus tract in combination with subcutaneous or intraarticular gas. However, plain X-rays may be negative in more than 50% of cases and may be of minimal diagnostic utility in acute infection [31]. Instead, conventional X-ray with the addition of arthrography or fistulography may drastically increase the diagnostic yield by illuminating infectious channels and accumulations [32,33]. Traditionally, more advanced imaging modalities such as CT and MRI were believed to be of limited use in evaluating the soft tissues immediately around a total joint prosthesis due to large amounts of metal artifact and image distortion. Recent developments, including metal artifact reduction sequence (MARS) MRI and three-dimensional reconstruction, allow for a much more detailed evaluation of periarticular structures and the presence of sinus tracts. However, given the dynamic nature of soft tissues and underlying infection, imaging studies may not provide sufficient evidence to verify the existence of a sinus tract as these may fluctuate in their patency and extent. Therefore, imaging modalities should not solely be relied upon for the identification of a sinus communicating with a joint prosthesis.

In summary, an established sinus tract or fistulous connection between a deep prosthetic joint and another space known to be colonized with pathogenic microorganisms should be considered tantamount to deep prosthetic infection. Although the literature does not provide clear guidelines regarding the time at which a draining wound becomes a sinus tract, it is clear that prolonged drainage from an arthroplasty wound increases the likelihood that deep infection will occur. While literature does not support the use of superficial sinus cultures to guide treatment of deep PJI, clinicians should rely on the presence of a sinus to justify surgical treatment. Therefore, any suspected connection between a deep prosthetic joint and an area colonized by pathogenic microorganisms should be considered seriously and evaluated thoroughly.

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2.2. DIAGNOSIS: LABORATORY TEST

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QUESTION 1: What serum test(s) have the best diagnostic accuracy for periprosthetic joint infection (PJI)? Does the combination of any number of tests increase the diagnostic accuracy?

RECOMMENDATION: Several serum biomarkers have been used as diagnostic tools for PJI with C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) being the most commonly-accepted screening tests. CRP and ESR are well-researched screening tests and have high sensitivity when used alone. Serum D-dimer for the diagnosis of PJI is being actively evaluated with encouraging early results. Combining serological tests have shown to improve diagnostic accuracy, but further work is needed to identify the optimal combination. It should also be noted that diagnosis of PJI cannot be based solely on serological tests at this time.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 5%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Compared to other invasive procedures. serological studies requires a blood draw which makes them attractive diagnostic tools as they are readily available and repeatable. However, diagnosing PJI based only on a single serum test or a combination of serum tests is challenging as no single serum test has 100% diagnostic accuracy [1]. Also, a literature review shows significant pitfalls while assessing best serological tests as most of the studies are retrospective and consist of highly selective patient sample with a long list of exclusions based on associated comorbidities and prior use of antibiotics [2]. Diagnostic accuracy of serological tests are also influenced by threshold values used, surgical trauma in early postoperative period, organism causing the PJI, concurrent antibiotic usage and associated comorbidities like inflammatory disorders, malignancy and concurrent infections [2–8].

Serum CRP and ESR are markers of systemic response to inflammation [9], and they are currently the most routinely used serological tests in PJI diagnosis. They are currently recommended as first-line screening tests for PJI and are part of diagnostic criteria suggested by 2013 International Consensus Meeting's Musculoskeletal Infection Society (MSIS) and American Academy of Orthopaedic Surgeons (AAOS) [10–13]. Current suggested thresholds are 1 mg/dl and 30 mm/hr for CRP and ESR, respectively. Utilizing recommended threshold value of 1 mg/dl and 30 mm/hr for CRP and ESR respectively, they have highly varying sensitivities and specificities. Huerfano et al. in a systematic review and a meta-analysis of 12 studies found that ESR had pooled sensitivity and specificity of 86% and 72.3%, respectively while the corresponding values for CRP were 86.9% and 78.6%, respectively. Their opinion was that in a low pretest probability situation a negative result for either of the above tests would be sufficient to rule out infection before revision surgery [14]. In another meta-analysis by Berbari et al., pooled sensitivity and specificity for ESR was 75% and 70%, and for CRP it was 88% and 74%, respectively [15]. In a recent meta-analysis of 25 studies, Yuan et al. reported that when 10 mg/L was used as the cutoff value, the pooled estimates for sensitivity, specificity and the area under the curve (AUC) for the CRP assay were 88% (95% confidence interval (CI) 86% to 90%), 73% (95% CI 71% to 75%), and 0.85, respectively.

As diagnostic tests, CRP and ESR tests have limitations to use before reimplantation and in patients with inflammatory diseases and during the early postoperative period [6,7,16]. In addition, use of prior systemic antibiotics may compromise their diagnostic value [4]. Also, it is important to consider that PJI can still exist in cases with normal serology test values especially when infection is caused by slow-growing organisms such as *Cutibacterium acnes (C. acnes)* (formerly *Propionibacterium acnes*) and coagulase-negative *Staphylococcus* [2,5].

In patients with inflammatory arthritis and chronic PJI, Cipriano et al. utilized threshold values of 30 mm/hr for ESR and 17 mg/L for CRP, and their results showed the AUC to be 0.850 and 0.851, respectively [16]. In another study with inflammatory arthritis patients, George et al. utilized a threshold value of 29.5 mm/h for ESR and 2.8 mg/dl for CRP to diagnose persistent infection in two-stage revision. Using above threshold levels, they found that sensitivity and specificity for ESR was around 64% and 77% and for CRP it was 64% and 90%, respectively. In their study, AUC for ESR and CRP was comparable at 0.74 and 0.81 [6]. In both studies, higher threshold levels for CRP was suggested to diagnose infection in patients with inflammatory arthritis.

In the acute postoperative period (less than six weeks from index surgery) ESR and CRP are usually elevated. ESR can be elevated for up to six weeks after surgery, and CRP can be elevated up to two weeks post-surgery [8]. In a retrospective study, Sang-Gyun et al., reviewed patients with suspected PJI three weeks post joint replacement and found CRP useful for diagnosis at a higher threshold value. Using a threshold value of 34.9 mg/L, their sensitivity and specificity of a CRP test were 100% and 90.3%, respectively. In their study, AUC for CRP was 0.981 [7]. Based on the results of prior studies, the proceedings of the 2013 International Consensus on PJI recommended a cutoff of CRP > 100 mg/L for diagnosis of acute postoperative PJI [10,13,17].

Elevation of serum white blood cell (WBC) count and neutrophil differential has been the hallmark for diagnosis of many infections. Serum WBC count, however, may not be a reliable test for the diagnosis of PJI. In a single institutional retrospective cohort study, the diagnostic cutoff point determined by receiver operating characteristic curve analysis was 7,800 cells/μL. With this threshold level serum, WBC had 55% sensitivity and 66% specificity. Utilizing serum neutrophil percentage at 68% as a criterion the sensitivity and specificity was 52% and 75% respectively [18]. A recent meta-analysis by Berberi et al. detected a pooled sensitivity of 45% and specificity of 87% for WBC count in the diagnosis of PJI [15]. Thus, serum WBC count and neutrophil differential could not be recommended as a diagnostic test for PJI.

The IL-6 is an inflammatory cytokine that is produced in response to infection or inflammation by monocytes and macrophages. IL-6 stimulates the production of major acute phase proteins, including CRP. It is significantly elevated in patients with PJI than in

aseptic loosening [19]. Shah et al., measured cytokines in the early preoperative period and found IL-6 levels rise at 6 hours post-surgery and these levels rapidly returned to normal in 48 hours [20]. These characteristics make IL-6 a potentially useful serum biomarker for PJI, especially in the early postoperative period. IL-6 levels seem to come back to normal relatively quickly after clearance of infection, therefore, this test may be much more useful in monitoring infection before reimplantation [21]. One must keep in mind that serum IL-6 can be raised in cases with polyethylene wear without evidence of infection [22].

In a meta-analysis based on three studies, Berbari et al., showed that the diagnostic odds ratio for serum IL-6 was 314.7 with pooled sensitivity and specificity at 97% and 91%, respectively [15]. In a recent meta-analysis based on 17 studies (11 studies with serum IL-6), Xie et al., found that pooled sensitivity and specificity of serum IL-6 were around 72% and 89%, respectively. In this meta-analysis pooled diagnostic odds ratio and the AUC was 20 and 0.83, respectively [23]. These results are comparable to CRP and ESR. Based on these results no definitive conclusion can be made currently, and further clinical trials are necessary before serum IL-6 could be component of routine PJI workup.

Procalcitonin (PCT) is a protein with 116 amino acids that is produced by the neuroendocrine cells and the parafollicular cells of the thyroid. The serum PCT level in healthy people without infection is extremely low and cannot be detected. Because the PCT level in blood increases when a bacterial infection occurs, serum PCT test has a high diagnostic accuracy for the identification of systemic infection [24]. However, the real diagnostic value of serum PCT for the detection of PJI is uncertain. In a systematic review based on 6 studies, Yoon et al. found that pooled sensitivity, specificity and AUC was 58%, 95% and 0.83, respectively [25]. In another meta-analysis by Xie et al., the pooled sensitivity was 53%, the pooled specificity was 92%, and the pooled diagnostic odds ratio was 13 for serum PCT [26]. Lack of sensitivity limits usefulness of procalcitonin as an optimal test for PJI diagnosis.

D-dimer, a fibrin degradation product, has been traditionally used as screening test for deep venous thrombosis (DVT). Multiple studies have shown that both systemic and local infections can result in fibrinolytic activity leading to increased D-dimer levels [27–29]. An animal study by Ribera et al., showed that fouls with septic arthritis had marked the elevation of synovial fluid D-dimer levels [30]. In a prospective study, Shahi et al. showed that D-dimer shows promise as a diagnostic serological marker in PJI with sensitivity and specificity of 89% and 93%, respectively, and in their study, D-dimer outperformed ESR and CRP in the diagnosis of PJI [31]. However, this is a single study, and further research is needed to confirm its superiority over ESR and CRP.

Other experimental and potential serological markers for PJI include advanced glycation endproduct levels like plasmatic soluble receptor for advanced glycation end products (sRAGE), thiobarbituric acid reactive substance (TBARS), lipopolysaccharide binding protein (LBP), Toll-Like Receptor 2 in Serum (TLR-2), Serum soluble urokinase-type plasminogen activator receptor (suPAR), Presepsin (also known as sCD14-ST, a subtype of the soluble form of CD14) and Soluble intercellular adhesion molecule-1 (ICAM-1) [32–38]. Although these markers have shown promise so far, further studies are needed to evaluate their role in the diagnosis of PJI.

Combining Tests

The literature review showed that combining serological test results can improve diagnostic accuracy, although definitive conclusions cannot be drawn due to conflicting results across the literature. Bottner et al. showed that utilizing both positive CRP (> 3.2mg/dl) and serum IL-6 levels (> 12 pg/ml) sensitivity improved to 100% and specificity improved to 86% [22]. Using different thresholds, Ettinger et al., combining positive serum IL-6 (> 5.2 pg/ml) and CRP (> 0.3mg/dl) demonstrated an increased specificity to 98.2% and diagnostic odds ratio to 168 [39]. In contrast, Buttaro et al. used a serum CRP level of 10 mg/L and IL-6 level of 10 pg/mL as the threshold, and identified the sensitivity, specificity, positive predicting value and negative predicting value of a combination of CRP and IL-6 to be 57%, 100%, 100% and 94%, respectively [40]. In another diagnostic model when either CRP or ESR results were positive it was shown that sensitivity (96% to 97.6%) improved significantly at the expense of specificity (51.5% to 58.5%) [41,42]. On the other hand, using a model where both CRP or ESR positive results specificity improved modestly by 78.8% to 89% and sensitivity was between 78.8% to 89% [41–43].

In conclusion and in the absence of conclusive evidence, it appears that serum CRP an ESR are still useful screening tests for diagnosis of PJI. Depending on the threshold chosen for each test, the causative organism for PJI, chronicity of infection and the presence of medical comorbidities, the sensitivity and specificity of these tests vary. There is a dire need for better serum tests for diagnosis of PJI and for optimal timing of reimplantation.

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QUESTION 2: Which patient-specific factors (i.e., inflammatory arthritis, immunocompromised state) influence the thresholds for serum and synovial markers in acute and chronic periprosthetic joint infection (PJI)?

RECOMMENDATION: There are currently no inflammatory arthritis-specific factors known to influence the thresholds for serum and synovial markers in PJIs. The literature on PJIs in inflammatory arthritis (IA) is sparse. While α-defensin is the best studied synovial biomarker, as with synovial white blood cell (WBC) count and C-reactive protein (CRP), there appears to be overlap in values limiting their utility in differentiating septic from aseptic effusions in patients with inflammatory arthritis.

LEVEL OF EVIDENCE: Limited due to small numbers

DELEGATE VOTE: Agree: 84%, Disagree: 7%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

PJI is a concerning complication of total joint arthroplasty and rapid and accurate diagnosis is critical to determine appropriate treatment [1]. However, differentiating between septic and aseptic failure continues to be a diagnostic challenge and is particularly problematic in patients with IA who, in the setting of PJI, have both systemic and intra-articular sources for increased inflammatory markers.

Synovial fluid biomarkers, like WBC count and percent of polymorphonuclear neutrophils (PMN), CRP, α-defensin, cytokines such as IL-6 and leukocyte esterase may be helpful for detection of PJI [2]. However, as with serum cytokines, synovial fluid cytokines have low specificity and may be abnormal in patients with immunological and inflammatory disease [3]. Synovial WBC count is included in

both the International Consensus's and Musculoskeletal Infection Society (MSIS) criteria of PJIs [4,5]. However, counts may be elevated in active disease or flares in IA patients. The α-defensin immunoassay, synovial Il-6 level, and leukocyte esterase have all been proposed for the diagnosis of PJI [6], but the utility in patients with IA is unclear. The aim of our systematic review is to evaluate serum and synovial fluid biomarkers and their efficacy at diagnosing PJI in patients with IA.

Our comprehensive literature search retrieved 20 papers that studied biomarkers in PJI and included patients with IA. Of the 21 studies included, 7 specifically addressed findings in IA patients and 14 included IA patients within a larger cohort. The following ranges of sensitivities and specificities for synovial biomarkers were investigated in three or more studies. These values reflect predictions of PJI versus aseptic failure: CRP elevation had a sensitivity ranging from 87.1 to 100% and a specificity of 28.85 to 97.7% [7–12]. WBC count elevation had a sensitivity of 60 to 91% and specificity of 51.4 to 94.3% [12–16]. IL-6 elevation had a sensitivity of 82 to 97% and specificity of 89 to 100% [8,10,14,17]. IL-8 elevation had a sensitivity of 75 to 95% and specificity of 64.71 to 100% [8,9,11,17]. α-defensin had a sensitivity of 97.3 to 100% and a specificity of 95.5 to 100% [10,11,18].

Of the six studies that specifically addressed IA patients [7,9,15,16,18], Cipriano et al. performed the only one that directly compared results for PJI in IA vs. non-IA patients and showed that values for ESR, CRP and synovial WBC count and PMN percentage in patients with IA have a lower optimal diagnostic threshold and lower specificity (Table 1). Median value for serum CRP from three studies are summarized (Table 2), and demonstrates higher serum CRP in PJI-IA than aseptic-IA patients, although these findings could not be pooled for meta-analysis due to methodological differences. Additional data provided by the authors [7,9] allowed us to further calculate the median value for serum CRP in non-IA patients with PJIs which were lower than those of PJI IA patients but higher than IA patients without infection.

Seven studies included data on α-defensin, [9–11,18–21] and three of these papers specifically provided α-defensin data on IA patients. Bonanzinga et al. reported on a cohort of 156 patients, including 9 patients with inflammatory disease. Of the nine IA patients, one had a PJI and had elevated α-defensin and CRP levels compared to uninfected inflammatory disease patients (Table 3). Overall, the α-defensin test showed one false-positive and four false-negatives. Erdemli et al. provided additional data on seven inflammatory arthritis patients included in their study. Two patients with PJI had rheumatoid arthritis (RA) and of five uninfected patients, one had systemic lupus erythematosus and four had RA. The α-defensin test was negative (< 0.00 ng/mL) for the two patients with PJI and RA [9]. The mean and median value of α-defensin for the aseptic group was 12.4 ng/mL and 15.0 ng/mL respectively. Lastly, Patridge et al.

TABLE 1. Cipriano et al. [16] outcomes summary

Test		Threshold	Sensitivity	Specificity
ESR	Non-IA	32 mm/hr	87.2%	67.1%
IA		30 mm/hr	94.4%	59.4%
CRP	Non-IA	15 mg/L	85.8%	83.4%
IA		17 mg/L	93.8%	70.3%
SFWBC	Non-IA	3,450 cells/μL	91.0%	93.0%
IA		3,444 cells/μL	88.2%	80.0%
SFPMN%	Non-IA	78%	95.5%	87.3%
IA		75%	100%	81.8%

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; IA, inflammatory arthritis; SFWBC, synovial fluid white blood cell count; SFPMN%, synovial fluid polymorphonuclear percentage

TABLE 2. Median values for serum CRP (mg/L)

Author	n	CRP PJI IA	n	CRP Aseptic-IA	n	CRP PJI non-IA
Tetreault [7]	5	68.3	8	19.1	27	45.15
Erdemeli [9]	2	26	6	3.56	36	25
Bonanzinga [18]	1	26.5	6	2.35	—	n/a

CRP, C-reactive protein; IA, inflammatory arthritis; PJA, periprosthetic joint infection

discuss a case report of a patient with acute gout who had a false positive α-defensin lateral assay Synovasure® test [19]. The results of the remaining four studies did not report on IA patients specifically, but included this population in their cohort (the results are summarized in Table 4).

Il-6 levels were addressed in six studies, but none of these studies reported outcomes on specifically IA patients [9,10,14,17,22]. Colvin et al. reported on leukocyte esterase test for PJIs but also did not report outcomes for IA patients [23]. Although both these tests show utility for predicting PJI they are untested in IA patients.

The available published studies addressing the diagnosis of PJI in patients with inflammatory arthritis is limited by small numbers. No synovial biomarker demonstrates high sensitivity and specificity for PJI in patients with IA. Diagnostic tests for synovial WBC count, serum CRP, α-defensin appear higher in patients with inflammatory arthritis, but there is overlap between values seen in patients with inflammatory disease who are not infected.

Serum ESR and CRP are known sensitive markers of PJI with poor specificity, however their use in the presence of IA is controversial owing to elevated basal levels that can potentially cause a false-positive result [16,24–26]. The combination of an elevated ESR and CRP with traditional thresholds has been shown to be a more accurate predictor of PJI than isolated elevations of ESR or CRP [24,25,27]. However, optimal threshold levels for these markers may vary for IA. Dizdaveric et al. found significantly higher mean levels of ESR and CRP in patients with IA compared with their non-inflammatory arthritis counterparts [28]. There is sparse literature on the topic and further studies are needed to elucidate whether the cutoff reference values are different in IA patients than in the general population. These thresholds can be affected by multiple factors including time of aspiration, effect of disease-modifying anti-rheumatic drugs (DMARDs) or other treatments, or stage of inflammatory condition (flared versus controlled disease).

It is important to note that adipose tissue can affect IL-6 levels [29], and thus these levels may be elevated in obese patients. Furthermore, metal corrosion can affect serum ESR and CRP levels as well as synovial alpha-defensin levels [18], making it difficult to diagnose PJI.

TABLE 3. Summary of Bonanzinga et al. [18] inflammatory patients

Inflammatory Disease	Infection Status	CRP (mg/L)	α-defensin (S/CO)
Eczema	Aseptic	0.94	0.2
Irregular antibodies	Aseptic	1.04	< 0.1
Crohn's Disease	Aseptic	0.59	< 0.1
RA	PJI	26.5	7.1
CLL	Aseptic	3.1	< 0.1
Psoriasis	Aseptic	9.77	< 0.1
Psoriasis	Aseptic	5.88	< 0.1
RA	Aseptic	1.67	< 0.1
SLE	Aseptic	3.03	< 0.1

CLL, chronic lymphatic leukemia; CRP, C-reactive protein; PJI, periprosthetic joint infection; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; S/CO, signal cutoff ratio

TABLE 4. Summary of α-defensin results

Study	Population	False Positive	False Negative	Sensitivity	Specificity
Martin [21]	14 cases, no IA distinction	2	1	80%	79%
Frangiamore [20]	116 cases, no IA distinction	2	1	n/a	n/a
Deirmengian [10]	95 cases, 11 IA	n/a	n/a	100	100
Deirmengian [11]	149 cases, 35 IA	5	1	97.3	95.5

IA, inflammatory arthritis

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QUESTION 3: Does prior use of antibiotics influence the accuracy of tests used to diagnose periprosthetic joint infection (PJI)?

RECOMMENDATION: Yes. The use of premature antibiotics can compromise the accuracy of the routine diagnostic tests that are used for PJI. We strongly urge the medical community to abstain from administration of antibiotics in patients with suspected PJI, unless the patient has significant systemic instability due to sepsis and following discussion with an orthopaedic surgeon.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 97%, Disagree: 2%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Diagnosis of PJI is currently one of the most challenging problems that the orthopaedic community is facing [1]. There is no absolute test and the available diagnostic tools are far from perfect. Cultures, for example, are negative in 7% to 12% of PJI patients [2–5]. Culture-negative PJIs can complicate the diagnostic work-up with added uncertainty.

According to the 2018 definition of PJI, major diagnostic criteria, those being a communicating sinus tract or two positive cultures, are the bedrock of the diagnosis [6]. Numerous studies have shown that administration of antibiotics is associated with higher rates of culture negative PJIs. Berbari et al. [3] reviewed 897 PJI cases, 60 (7%) of which had negative cultures. Of the culture-negatives, 32 (53%)

received a prior course of antimicrobial agents. Authors concluded that culture negative PJIs are more common among patients who receive an antimicrobial therapy prior to obtaining samples for culturing. Parvizi et al. [7], in their extensive review of culture negative PJIs, indicated that administration of therapeutic antibiotics prior to sampling is the main cause of negative cultures.

Other diagnostic tests are also affected by therapeutic antibiotics. Shahi et al. [8] did a retrospective study on 182 PJI patients (confirmed as per the Musculoskeletal Infection Society (MSIS) criteria) of which 65 patients received antibiotics within 2 weeks prior to diagnostic workups for PJI. Their results were in line with the previous studies and showed that PJI patients who received premature antibiotics have significantly higher rates of negative cultures. Moreover, authors showed that the median for all the routine diagnostic tests (serum erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and synovial fluid white blood cell (WBC) count, polymorphonuclear (PMN) leukocyte percentage) were statistically lower when antibiotics were administered. They also reported that the sensitivity of serum ESR, CRP and synovial PMN leukocyte percentage were statistically lower when antibiotics were used.

In an attempt to find a solution for this issue, the authors conducted another study with a separate cohort [9]. A retrospective study of 106 hip and knee arthroplasties with MSIS defined PJIs used cases from four different centers. Of the 106 patients in this study, 30 (28%) were treated with antibiotics for PJI before diagnostic workups, and 76 (72%) did not receive antibiotics treatments prior to the diagnostic work-up. Sensitivity of serum ESR and CRP, synovial WBC, percentage PMN and alpha-defensin were compared between the two groups using the MSIS recommended thresholds. All the tests had significantly lower sensitivities when therapeutic antibiotics were used except for synovial fluid alpha-defensin. Authors recommended that in case of a complicated patient, who is suspected for PJI and has received either oral (PO) or intraveneous (IV) antibiotics, synovial fluid alpha-defensin test can be used to help with the diagnosis.

Use of antibiotics prior to a definite diagnosis of PJI is a major clinical decision that can significantly complicate the diagnostic process. We strongly urge the medical community to abstain from administration of any forms of antibiotics prior to reaching a definite diagnosis for PJI, unless the patient has significant systemic instability due to sepsis. As of now, revision arthroplasty is the standard of care for patients with PJI and administration of therapeutic antibiotics prior to surgery have not been shown to have any benefits for these patients. It is imperative to distinguish between prophylactic antibiotics that are administered within two hours prior to the surgery and therapeutic antibiotics that are administered with an intention to treat PJI. Prophylactic antibiotics have been shown to have no effect on the intraoperative culture yield [10,11].

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QUESTION 4: Does the type of organism (i.e., fungi, *C. acnes*, *S. aureus*) influence the thresholds for serum and synovial markers in acute and chronic periprosthetic joint infection (PJI)?

RECOMMENDATION: Yes. Emerging data suggests that the type of organism influences the diagnostic thresholds for most serum and synovial biomarkers in the diagnosis of acute and chronic PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Diagnosis of PJI is currently a challenging process. There is no absolute diagnostic test and clinicians thus must rely on a combination of findings. The American Academy of Orthopaedic Surgeons (AAOS) [1,2] and the International Consensus Meeting (ICM) on PJI [3] currently recommend the serological markers of serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as the first line tests due to their reported high sensitivity in patients with suspected PJI. In addition, synovial white blood cell (WBC) counts, synovial polymorphonuclear percentage (PMN%) and leukocyte esterase (LE) will be frequently obtained, through aspiration, if there is high clinical suspicion for infection or if there is an elevation in the serological markers. Other serum and synovial biomarkers are

used to make the diagnosis of PJI including serum interleukin-6 (IL-6), procalcitonin, D-dimer, tumor necrosis factor alpha (TNF-a), intercellular adhesion molecule-1 and lipopolysaccharide-binding protein. Synovial markers include WBC count, PMN%, CRP, IL-6, interleukin 8, LE and alpha-defensin, among others [4,5]. In general, synovial fluid biomarkers are considered to have superior accuracy when compared to serum biomarkers [6–9].

While each organism varies in virulence to elicit an inflammatory response, the aforementioned biomarkers are also dependent on the host's ability to mount a response [10] and recent studies have suggested that they may be influenced by a variety of factors, including the use of antibiotics [11].

While antibiotics can reduce the levels of these inflammatory markers, it is suspected that the infecting organism may influence the levels of these markers depending on the organism's ability to elicit an immune response in the host. Thus, low virulence organisms, such as *C. acnes* and coagulase-negative *Staphylococcus* (CNS) may demonstrate lower levels of inflammatory markers. If less-virulent organisms produce a less-robust inflammatory response, it is reasonable to expect that serum and synovial markers for inflammation may be lower as well and have a higher false negative rate when using traditional cutoffs for diagnosing PJI [12]. If this is the case, one would expect that differing thresholds are needed for diagnostic criteria. Two recently-published investigations highlight this issue. One study demonstrated that synovial CRP levels were dependent on the infecting organism and that false negative results were more likely for less virulent organisms such *as S. epidermidis* and yeast [13]. Another study reported that seronegative PJI was common with less-virulent infecting organism such as *Staphylococcus epidermidis, C. acnes, actinomyces, corynybacterium, candida* and *mycobacterium* [14].

Recent data from the Rothman Institute demonstrates that organism type does indeed influence serum and synovial biomarker levels [15]. The authors of the study performed a retrospective review of all PJI cases over a 15-year period to determine whether biomarker levels differ among organisms and to identify new cutoff values for biomarkers for each organism type. The results of the study found that more traditionally virulent organisms, such as resistant organisms or *S. aureus*, result in higher inflammatory markers while less virulent organisms and culture-negative cases demonstrated lower levels. The authors observed similar results for synovial markers, WBC and PMN%. Thus, the particular infecting organism influences the false negative rate and the levels of routine synovial and serum tests for diagnosing PJI. New cutoff values were determined for each biomarker predicting PJI and stratified by organism type. The values were variable and highly dependent on the organism. Thus, it is important to consider clinical suspicion for diagnosing PJI as the accuracy of serum and synovial inflammatory markers are dependent on the infecting organism. Of note, this is especially true for CNS and for culture-negative infections as serum ESR, CRP, synovial WBC and PMN% are generally much lower for these cases and thus have lower cutoff values. Given that the sensitivity is low for certain organisms, it is important for surgeons to be cognizant that there may be a higher rate of false negatives with certain organisms.

While the literature is marginal given the large sample size needed to stratify the accuracy of diagnostic laboratory values by organism, several studies have suggested that the sensitivity of diagnostic tests are dependent on the organism. Deirmengian et al. [13] demonstrated that the median synovial fluid CRP level was significantly lower for less-virulent organisms, when compared to those organisms classified as virulent (15.10 mg/L vs. 32.70 mg/L, $p < .0001$). Perez-Prieto et al. [16] also demonstrated that CRP and ESR may be falsely negative in up to 32% and 23% of PJIs, respectively. In this study, the clear majority of these patients' cultures grew low-virulence organisms, CNS, or *C. acnes*. Similarly, in our study [17] we found that inflammatory markers were lower in the serum in patients infected with less virulent organisms as well as in culture-negative cases.

Certain organisms may elicit a weak host response whereas others mount a much more robust response, which may help explain why the amount of gross purulence discovered intraoperatively may differ depending on the bacterial organism. A study by Alijanipour et al. [18] demonstrated that intraoperative purulence was more commonly found in PJI caused by *streptococcus* spp. (88%) and *S. aureus* (85%) compared with CNS (73%) and gram-negative bacteria (73%, $p = 0.04$). Although the orthopaedic literature does not have much discrete data on the effect of organism virulence on biomarker levels, we do see frequent implications of low virulence organisms, such as *C. acnes*, in shoulder arthroplasty infection. It has been shown that ESR and CRP have poor sensitivity to detect prosthetic shoulder infection when using previously-established cutoffs of 30 mm per hour or 10 mg/L, respectively [19]. This is presumably due to the low virulence of *C. acnes* and the need for optimized cutoff values for this particular organism implicated in prosthetic infections. Similarly, in our study we see that the biomarker sensitivities differ among organisms and thus optimal cutoff values vary based on the organism growing.

However, not all markers are affected by organism type. Neutrophils in the synovial fluid secrete specific proteins in response to infection. These proteins, such as alpha-defensin, have shown sensitivity and specificity above 96% for the diagnosis of PJI [6,20,21]. A large-scale study reviewed the results of 1,937 samples that simultaneously had a synovial fluid culture performed [8]. The organisms recovered from 244 alpha-defensin positive, culture-positive fluids were recorded and grouped based on characteristics such as Gram stain, species, virulence, oral pathogenicity and source joint. Alpha-defensin negative samples served as uninfected controls. The alpha-defensin test for PJI was positive in the setting of a wide spectrum of organisms typically causing PJI. There was no difference in the magnitude of the alpha-defensin level regardless of Gram stain characteristics, specific organism, virulence, oral or non-oral pathogen or anatomic source. The test provides consistent results regardless of the organism type, Gram stain, species or virulence of the organism, and could be considered a standard diagnostic tool in the evaluation for PJI whenever synovial fluid is aspirated for a PJI work-up.

There is paucity of literature on fungal and acid-fast PJIs due to the rarity of such organisms. Fungal PJIs only represent 1% of PJIs [22]. Early knowledge of the microbe involved would aid in selecting appropriate antimicrobial therapy and would yield better treatment outcomes. The characteristics of systemic inflammatory markers in patients with fungal PJIs have not been fully assessed. In a single center review of 44 patients with culture-positive diagnosed fungal PJIs, the mean values for C-reactive protein and ESR were compared with 59 patients with bacterial PJI, including coagulase-negative *Staphylococcus* species, *Staphylococcus aureus*, *Escherichia coli* and *Streptococcus species* [23]. The mean ESR for fungal and bacterial PJIs were 40 mm per hour (95% confidence interval (CI); 30, 50 mm per hour) and 41 mm per hour (95% CI 33, 49 mm per hr), respectively ($p = 0.61$). The mean CRP values for fungal and bacterial PJIs were 42 mg/l (95% CI 22, 62 mg/L) and 65 mg/L (95% CI 43, 88 mg/L), respectively ($p = 0.42$). Systemic inflammatory markers do not discriminate between bacterial and fungal infections. Due to the rare nature of fungal PJIs, multicenter collaborations are a possible research avenue to further study this question.

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QUESTION 5: What is the diagnostic accuracy of intraoperative Gram stain for the diagnosis of surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Intraoperative Gram stain is an unreliable test to diagnose PJI. It carries a low sensitivity and high rate of false negatives. Therefore, it is not recommended for the diagnosis of SSI/PJI.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 95%, Disagree: 4%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Gram stain has become a routine component in the processing of specimens sent for culture. Over the past two decades, concerns have been raised over the diagnostic accuracy of Gram stain to detect a PJI in the setting of painful or failed total hip and knee arthroplasty (THA and TKA) [1–5].

In general, the literature has demonstrated significantly poor results regarding the ability of Gram stain to rule out PJI. Table 1 is a summary of the published diagnostic values regarding the role of Gram stain in the setting of revision total joint arthroplasty (TJA).

Notwithstanding the poor diagnostic accuracy of Gram stain, we must consider the cost associated with routinely performing a Gram stain. Della Valle et al. pointed out the cost of a single Gram stain was $14.30, which combined with the poor sensitivity lead to a cost of $598.85 per true-positive result [2]. Therefore, we would strongly recommend for the universal abandonment of Gram stain in the diagnosis and management of PJI.

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TABLE 1. Summary of the published diagnostic values regarding the role of Gram stain in the setting of revision TJA

Author	Procedure	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Kraemer [6]	Revision THA	23%	100%	100%	81%
Chimento [3]	Revision TJA	0%	0%	0%	0%
Barrack [4]	Revision TKA	10%	100%	Not calculated	Not calculated
Atkins [5]	Revision TJA	6%	99.7%	Not calculated	Not calculated
Della Valle [2]	Revision TJA	14.7%	98.8%	71.4%	85.4%
Spangehl [1]	Revision THA	19%	98%	63%	89%
Banit [7]	Revision TJA	43%	100%	Not calculated	Not calculated
Ko [8]	Revision TJA	0%	0%	0%	0%
Parvizi [9]	Revision TJA	35%	97%	94%	54%
Parvizi [9]	Revision TJA	22%	100%	100%	50%
Ghanem [10]	Revision THA	31%	100%	100%	79%
Ghanem [10]	Revision TKA	30%	100%	98%	70%
Morgan [11]	Revision TKA	27%	99.9%	98.5%	79%
Johnson [12]	Revision THA	9.8%	100%	100%	62%
Oethinger [13]	Revision TJA	23%	92%	Not calculated	Not calculated
Oethinger [13]	Revision TJA	9%	99%	Not calculated	Not calculated
Zywiel [14]	Revision TKA	7%	99%	92%	57%

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QUESTION 6: Is there a role for procalcitonin (PCT) blood test in the diagnosis of surgical site infection/periprosthetic joint infection (SSI/PJI) in orthopaedic patients?

RECOMMENDATION: No. The literature demonstrates the existence of biomarkers with superior diagnostic value compared to a serum PCT blood test in determining the presence of infection in orthopaedic patients.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 92%, Disagree: 3%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

PJI remains one of the most challenging complications that can result from total joint arthroplasty (TJA). Because the symptoms of PJI are often non-specific and there is no gold standard threshold or criteria for the currently-available laboratory tests, PJI is difficult to diagnose with precision [1,2]. Therefore, it remains imperative in determining the most valuable markers for use in diagnosing PJI in order to expedite treatment for this patient population. For example, serum biomarkers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and white blood cell (WBC) count are not sufficiently specific to diagnose PJI on their own [3]. Numerous studies focusing on the diagnostic accuracy of novel biomarkers have suggested that the PCT serum blood test may be a useful biomarker because of its rapid assessment and high specificity [4–6].

A meta-analysis by Shen et al. in 2013 determined that serum PCT had some benefit for use, but only as a diagnostic tool for determining patients with septic arthritis and/or osteomyelitis [7]. Additionally, Bottner et al. and Worthington et al. also suggested that serum PCT was only an accurate marker for systemic bacterial infections and Bottner et al. additionally endorsed it as a diagnostic tool because of its heightened specificity. Bottner et al. recommended that PCT had limited usefulness as only being a confirmatory test for systemic infection and not PJI and only after screening with IL-6 and CRP simultaneously because of its high specificity (.98) and low sensitivity (.33) [8]. A small prospective study by Yuan et al. was conducted examining 74 total hip arthroplasty (THA) revision cases and compared preoperative values of PCT with WBC counts and CRP in order to determine which test was the most valuable diagnostic marker [9]. Respectively, the areas under the curve (AUCs) for serum PCT, CRP and WBC count were 0.851 (95% confidence interval (CI) 0.773 to 0.929), 0.830 (95% CI 0.751 to 0.910), and 0.633 (95% CI 0.518 to 0.747) showing that PCT and CRP were significantly greater in diagnostic accuracy than WBC count ($p < 0.05$). The population size of this study was relatively small and there was no significant difference ($p = 0.0367$) in the diagnostic value of PCT and CRP.

In contrast, Worthington et al. examined predictors of infection in revision TJA and determined that PCT was not valuable in differentiating patients with aseptic loosening from those with septic loosening and they showed the greater diagnostic ability of CRP ($p = 0.0001$), ESR ($p = 0.0001$) and WBC ($p = 0.003$) signals as they were all significantly higher in patients undergoing revision for septic loosening [10]. The higher quality in combining IL-6 with CRP as a diagnostic marker in comparison to PCT was also demonstrated by Ettinger et al. as they inspected revision patients and scrutinized them for either having a low-grade joint infection or aseptic joint failure [11].

Similarly, Sousa et al. also showed that PCT synovial fluid tests showed no difference in patients with PJI and those without PJI [12]. These studies confirmed that the usefulness of PCT testing lies with serum testing and not in synovial fluid analysis for patients.

Additionally, Drago et al. showed that the levels of serum PCT did not differ between patients with PJI and those without PJI and determined that only IL-6 was an accurate diagnostic marker of PJI [13]. Equally, a recent meta-analysis by Yoon et al. in 2018 compared PCT with IL-6 in its ability to diagnose PJI [14]. They also demonstrated that IL-6 was far superior in its diagnostic ability compared to serum PCT. They further recommended that PCT was not useful as a rule-out diagnostic tool owing to its high negative likelihood ratio and that IL-6 had a greater diagnostic value in comparison to PCT because of its higher AUC of 0.93 (95% CI 0.91 to 0.95) vs. an AUC of 0.83 (95% CI 0.79 to 0.86) for PCT.

In 2017, a meta-analysis performed by Xie et al. compared the PJI diagnosing utility of α-defensin with PCT and found that α-defensin was also superior to serum PCT with regard to specificity (.95 vs. .92), positive likelihood ratio (19.6 vs. 6.8) and AUC (.99 vs. .76) [15]. This showed that α-defensin was a superior biomarker in the diagnosis of PJI by comparison to serum PCT.

The majority of the aforementioned studies provide irrefutable evidence that serum PCT does not have utility in its diagnostic ability in detecting PJI in arthroplasty patients. However, the same literature provides evidence that there are far superior tests in providing a diagnosis of PJI in the same setting. In summary, considering the insufficient support in the literature for the use of PCT in the diagnosis of PJI, we recommend that other diagnostic tests that have superior value be used in its place.

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2.3. DIAGNOSIS: PATHOGEN ISOLATION, CULTURE

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QUESTION 1: What is the optimal methodology for obtaining intraoperative cultures?

RECOMMENDATION: Each tissue sample should be collected using separate sterile instruments and transferred directly into culture bottles and transferred to the laboratory as soon as possible. A minimum of three and maximum of five intraoperative cultures (periprosthetic tissue) should be obtained. It is preferable that samples are obtained from the implant-bone interface, whenever possible. Swab cultures should be avoided due to their poor diagnostic accuracy. Synovial fluid should also be collected and placed into blood culture bottles, where possible.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The accurate identification of the microorganism(s) responsible for periprosthetic joint infection (PJI) is a pivotal step in the management of this complication. In addition to confirming the diagnosis, this will enable the administration of specific antibiotics to help optimize infection eradication and joint salvage. Failure to identify the correct microorganism can result in potentially toxic, expensive treatments, as well as possible failure of PJI erdication [1,2]. Consensus is therefore needed to establish standard methods for intraoperative sampling in order to determine the best type of samples to be cultured, the optimal number of tissue specimens and the most suitable method of sample transportation to the laboratory.

With regards to the method of obtaining intraoperative cultures, previous studies have demonstrated that tissue cultures have a higher sensitivity and specificity than swab cultures for diagnosing PJI and therefore swabs should be avoided [3–5]. The most suitable intraoperative samples consist of tissue samples, synovial fluid and prosthetic components or entire prostheses. Each tissue sample should be collected using separate surgical instruments in order to prevent sample cross contamination and to obtain true independent samples [6]. The biopsies should be taken from the synovial lining and periprosthetic tissues with the aim of targeting visibly inflamed or abnormal tissue [7]. Preference should be given to sampling the membrane at the implant-bone interface as such samples are most likely to yield positive results [8–10]. When histological examination of the periarticular tissues is planned, it is helpful to obtain paired samples for histopathological and microbiological examination from the same area in order to enable correlation of results.

The optimal number of intraoperative specimens required to maximize the likelihood of identifying the infecting organism has been extensively investigated. Earlier studies suggested that the highest sensitivity and specificity was achieved by obtaining five or six samples [11–15]. Recent studies have used different culture media in an attempt to reduce the number of samples required and thereby decrease the technical and financial impact of this diagnostic modality. In a prospective multicenter study, Bemer et al. demonstrated that the minimum number of samples required to confirm PJI daignosis can be decreased to four, as long as each sample is cultured using three different media, including a blood culture bottle [10]. Peel et al. [16] also demonstrated that a high level of accuracy for PJI diagnosis is obtained when three periprosthetic tissue specimens are inoculated into blood culture bottles, or four periprosthetic tissue specimens are cultured using standard plate and broth techniques. Gandhi et al. [17] also used receiver-operating characteristic (ROC) curve analysis to demonstrate that the optimal sample number necessary to yield a positive test result was four. We therefore recommend that four tissue samples are obtained to provide the best sensitivity without compromising specificity.

Whenever possible, synovial fluid should be sent for analysis as it can be used for both culture as well as the detection of commonly-used PJI biomarkers [18]. With regards to detection of the infecting organism, the sensitivity of the synovial fluid inoculated into blood culture bottles is higher than traditional culture [4,19,20].

There are no conclusive studies evaluating the performance of transport media for orthopaedic samples as the performance of transportation systems differed depending on temperature, holding time and bacterial strains. In general, good preservation of samples has been reported for media held at 4°C [5]. Specimens should reach the laboratory as soon as possible and experimental models suggest that there is a significant loss of the bacterial yield after a six-hour delay [21]. The latter study suggested that the optimal time for samples to reach the laboratory is approximately two hours.

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QUESTION 2: What methods can be utilized to increase the diagnostic yield of microbiological culture in surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: At least four intraoperative cultures should be obtained to increase the diagnostic yield. There is limited evidence to suggest that cultures from the synovium, synovial fluid or tissue in contact with prosthesis may be more likely to identify a pathogen. The samples should be inoculated in blood culture bottles and the addition of enriched media (such as a chocolate agar plate and Schaedler broth) or bead mill processing broth may also augment yield.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 86%, Disagree: 9%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Identifying an organism from microbiological culture is critical for both the diagnosis and treatment of SSI and PJI [1–3]. Two positive cultures from the same joint identifying the same organism by tissue or fluid remains as one of the major criteria for the diagnosis of PJI in total joint arthroplasty (TJA). This qualifies as a "major" criterion in both 2013 and 2018 definitions of PJI [2,4]. However, in 7 to 35% [5–9] of patients, no organisms can be isolated despite meeting other criteria for infection, which defines "culture-negative" PJI patients [3]. In general, and particularly for this cohort of patients, optimizing culture yield can help determine type of surgical procedure, antibiotic therapy and likelihood of treatment success.

Methods of optimizing culture growth have been divided into preoperative, intraoperative and postoperative measures. With regard to preoperative measures, the American Academy of Orthopaedic Surgeons' Clinical Practice Guidelines (AAOS CPG) recommends aspirating a joint for culture at least two weeks following the last administration of antibiotics (moderate recommendation) [1]. If growth is unsuccessful initially, a repeat aspirate is recommended (consensus recommendation for knee, moderate for hip). Finally, if the diagnosis of PJI is suspected but not confirmed, holding antibiotic treatment is recommended in an attempt to identify an organism pre- or intraoperatively (strong recommendation) [1]. Intraoperative measures for optimizing culture growth include obtaining multiple cultures prior to irrigation and obtaining cultures from representative areas (i.e., intramedullary, implant interface). The samples for culture should also be obtained using a clean instrument and transferred immediately to the culture bottle for transport. The culture samples obtained should also be transported to the laboratory as soon as collection is complete.

Postoperative measures include choice of growth medium, bead mill processing, timely delivery to and processing by the laboratory, use of sonication and culture duration. The scope of this question will address the following: What is the right number of intraoperative cultures, what type of cultures should be obtained, which areas should be sampled, does bead mill processing increase yield and what is the best growth medium. The remainder of the measures to optimize growth are covered by other International Consensus Meeting (ICM) questions.

The AAOS CPG recommends that multiple cultures be obtained at the time of surgery (strong recommendation), but no number was provided. The 2013 ICM recommended that three to five cultures be taken in the setting of suspected or uncertain PJI (strong consensus) [10]. Previous studies recommended that five cultures be obtained [11–13] but Atkins et al. were the first to evaluate this prospectively and perform statistical analysis. They examined cultures grown from 297 revision arthroplasties and found that 5 to 6 cultures increased the likelihood of diagnosis [14]. In 2016, Bémer et al. published a prospective, multicenter study that found using four culture samples on three different growth media was a highly reliable and cost-saving approach to PJI diagnosis [15]. Gandhi et al. corroborated these results by examining 74 PJI patients meeting Musculoskeletal Infection Society (MSIS) criteria [16]. They found that the optimal number of cultures needed to yield a positive test result was four (specificity = 0.61 and sensitivity = 0.63) and concluded that increasing the number of samples increased sensitivity but reduced specificity [16]. Finally, Peel et al. also determined that a minimum of four cultures were optimal to achieve growth with conventional means but a minimum of only three cultures were required when using blood culture bottles [17]. Some authors have advocated up to 10 cultures in the setting of prior antibiotic use and less virulent organisms [18] but these situations may be ideal for the use of emerging technologies such as next generation sequencing [19].

With regard to how samples should be obtained, studies are mixed on whether synovial fluid culture is superior to tissue culture [15,16,20,21]. However, both are often obtained simultaneously in clinical practice and in combination increase the sensitivity for diagnosis [20]. Multiple studies have demonstrated that swabs are not a reliable culture method intraoperatively [7,22]. Due to their high rate of false-negative and false-positives [23], their use is strongly recommended against by the 2013 ICM [10]. It is often stated that cultures should be removed sharply with a scalpel, handled with clean instruments and placed directly into the sterile container. However, to the authors' knowledge, no studies have investigated the role of the technique to obtain the samples and culture yield.

It is often recommended that cultures be obtained from the intramedullary canal and bone-implant interface [24]. However, Gandhi et al. investigated the role of a "best culture." This is a practice used to identify a promising specimen from anywhere in the infected joint that should undergo additional testing (i.e., fungal and mycobacterial) beyond routine aerobic and anaerobic cultures [16]. Despite being a visually appealing specimen, this "best culture" practice did not increase the likelihood of growth [16]. In addition, Bémer et al. in a multicenter prospective study found the highest rates of culture positivity from synovial fluid 91.7%, followed by tissue in contact with implant material (91.5%) whereas bone samples had the lowest rates of positive cultures (76.6-87.1%) [15].

Once a culture is obtained, but prior to inoculation, a process known as bead mill processing may also be used. The process involves placing tissue specimens into sterile vials, adding a small amount of sterile water and beads (glass or metal) and adding mechanized agitation (bead mill) [15,25]. One study has reported improvements in PJI diagnosis when using this technique [25]. Another prospective, multicenter study utilized this method and also found higher rates of bacteriologically documented PJI than reported previously in the literature [15].

The use of alternate culture media has also been described to optimize culture growth. Hughes et al. reviewed 805 synovial fluid samples from patients suspected of having septic arthritis [26]. The culture results obtained with a blood culture bottle were compared to those obtained by a conventional agar plate method. The blood culture method identified significantly more pathogens and fewer contaminants compared to the conventional method [26]. Similarly, Font-Vizcarra et al. retrospectively reviewed 87 cases of PJI in 2010 [7]. They compared culture growth of synovial fluid inoculated in blood culture bottles to periprosthetic tissue and swab samples in standard media. Not only did the synovial fluid in blood culture bottles have a higher rate of positivity, this method also had higher sensitivity, specificity, and positive and negative predictive values for diagnosis of PJI when compared with standard tissue and swab samples [7]. Subsequent PJI studies have also demonstrated that cultures of periprosthetic tissue in blood culture bottles increases culture yield compared to swabs [27], standard agar/broth [28,29] and is similar in sensitivity to sonication [30].

Finally, aside from using blood culture bottles, enriched or organism specific medial has also been reported. When suspecting a fungal, zoonotic bacteria, mycobacterium or other unusual microorganisms, routine bacterial and anaerobic cultures will often fail to yield the pathogens [31]. The laboratory should be alerted when these organisms are suspected to avoid accidental exposure and the right media can be chosen such as brain-heart infusion, trypticase soy broth and chocolate agars [31]. Bémer et al. investigated the question of what is the best growth media and found that the most efficient means to identify PJI per their definition was obtained with a combination of three different culture media: a blood culture bottle, a chocolate agar plate and Schaedler broth [15]. The authors also reported that the chocolate agar plate was more sensitive than the anaerobic agar plate, particularly for the anaerobe *C. acnes* [15].

In conclusion, there is evidence to support the use of blood culture bottles, obtaining at least four intraoperative cultures (including synovial fluid and periprosthetic tissue), bead mill processing and enriched media to increase diagnostic yield of microbiological culture in SSI/PJI. Of these, the most studied methods include the ideal culture number and use of blood culture bottles (moderate evidence). The remainder of the interventions listed currently have limited evidence.

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QUESTION 3: What is the optimal time for culture processing of tissue or synovial aspirate samples? How long should routine cultures be kept before declared negative?

RECOMMENDATION: Cultures should be maintained for a period of five to seven days. In cases of suspected periprosthetic joint infection (PJI) with low-virulence organisms or if preoperative cultures have proven to be negative and there is a high clinical suspicion for PJI (culture-negative PJI), the cultures should be maintained from 14 to 21 days.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 87%, Disagree: 12%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

It is believed that the majority of common infecting organisms can be isolated within a few days of conventional culture. Additionally, there is currently no reason to extend the culture duration in patients in whom the infecting organism has been isolated preoperatively. Research has focused on the incubation period for samples from patients with suspected PJI, culture negative cases and patients who may be infected with low-virulence organisms, such as *C. acnes* and anaerobes. Unfortunately, there is no consensus on an appropriate culture time, although identifying the responsible infectious agent is critical in PJI [1].

There exists a notion that longer incubation times may increase the possibility of detecting contaminants and thus false positives [2]. However, numerous studies have demonstrated that extending culture time to two weeks significantly increases the culture sensitivity without increasing the risk for the growth of contaminants [1–5]. Currently, there is no evidence determining the cost-effectiveness associated with holding cultures for one week versus two weeks. Besides the matter of cost, it remains critical that cultures are held for an adequate amount of time in an effort to isolate any potential pathogen for even cases that are presumed aseptic [6,7].

Most tissue or synovial cultures are incubated for five days or less [8], however, there are studies underlying the importance of extending this period [1,5,9]. Butler-Wu et al. tried to identify the optimum culture conditions for recovery of *C. acnes* from PJI specimens [5]. They applied 28-day culture incubation to all specimens from 198 revision arthroplasties and found that minimum 13-day culture incubation for both aerobic and anaerobic cultures is necessary for diagnosing *C. acnes*. Incubation beyond this period was non-diagnostic for *C. acnes* isolates. Schaffer et al. proposed that microbiological culture should be held for 14 days to diagnose infection in patients after conducting a large prospective study, in which tissue samples from 284 patients were cultured [1]. Although the median time to diagnosis of a suspected organism was only 4 days, additional organisms causing PJI were grown up to 13 days later, further highlighting the polymicrobrial nature of PJI. Comparing early versus late detected organisms, they demonstrated that the early group was composed of staphylococci, enterococci, etreptococci and enterobacteria. These organisms grew within the first seven days of culture. The late group, growing predominantly from 7 to 14 days, exhibited growth from Propionibacterium species, aerobic gram-positive bacilli and *Peptostreptococcus* species.

Neut et al. evaluated a cohort of 22 patients with suspected septic loosening. They concluded that by prolonging the culture time to 7 days, it increased the detection rate of infectious bacteria from 41% to 64% [4]. Bossard et al. recommended that culture specimens should be kept for at least 10 days to detect *C. acnes* [10]. In their retrospective study examining 70 *C. acnes* infections, they found that in reducing the culture period to 7 days, diagnosis of PJI would have been missed in 21.4% of the cases. Despite their recommendation of a 10-day culture period, 6% of these *C. acnes* infections were identified outside the 10-day culture period. The similar conclusion about *C. acnes* was made by Framgiamore et al. who showed that 14% of the culture-positive cases were detected after day 7 in their review of 46 cases [11].

Additionally, there is literature proposing that a prolonged period of incubation (up to 21 days) is required to minimize the culture-negative PJI rate [12]. Parvizi et al. proposed that cultures should be kept for at least 14 days and if no microorganism is isolated, an additional 7 days of incubation may be required. An additional seven days of incubation may allow for the isolation of slow-growing organisms such as Mycobacterium species and fungi [12]. Utilizing a prolonged incubation period may be useful for cases where no organism is identified preoperatively.

Novel techniques have emerged to increase detection rates and minimize the culture period required in the diagnosis of PJI. In a prospective laboratory study over a seven-month period, tissue samples were taken from patients with suspected PJI [13]. All samples were cultured for 14 days, using a BD BACTEC™ instrumented blood culture system. All but 1 out of the 66 culture-positive cases of PJI was detected within 3 days of incubation. The use of blood culture bottles was valuable for increasing the diagnostic sensitivity for PJI. A more recent study evaluated culture time for anaerobes and proposed a modern laboratory procedure that could improve detection and shorten culture time [14]. They showed that all pathogens could be identified within six days using a highly sensitive media (supplemented liver thioglycollate broth) and with direct identification by matrix-assisted laser desorption/ionization (MALDI-TOF).

To date, there are numerous techniques and methodologies utilized in conventional culture. Current literature suggests that cultures should be kept and processed on the basis of the infecting organism. Cultures should be processed and kept for at least five days. In cases of suspected PJI with low virulence organisms or if preoperative cultures have proven to be negative and there is a high clinical suspicion for PJI, cultures should be maintained for at least 14 to 21 days.

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QUESTION 4: What is the recommended standardized laboratory culture protocol to minimize differences between medical centers?

RECOMMENDATION: Based on current guidelines from the Infectious Disease Society of America (IDSA), specimens for culture should be transported in sterile containers at room temperature and processed promptly within a two-hour window to limit specimen contamination or desiccation and subsequent death from nutrient deprivation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 3%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

At the present time, clinical microbiological laboratories utilize various approaches including molecular and classic culture methodologies in order to properly detect pathogenic microorganisms. However, culture remains to be the current preferred method in identification and subsequent classification of the infective pathogens. The practices in place are essential for assuring the correct determination of sensitivity and suitable treatment for patients following identification of the pathogen that led to surgical site infection (SSI) and/or periprosthetic joint infection (PJI). Standard protocols have been implemented for microbiological laboratories serving both large academic medical centers and smaller community programs in order to maintain equitable results and a minimum threshold for the quality of specimen culture and subsequently the care of patients [1].

There are a multitude of factors that should be understood when considering the standardization of culture procedures. Culture yield is influenced by laboratory plating technique, the transport vehicle of the specimen, the time frame before reaching nutrient, the type of growth enabling media used and numerous other factors. A recommendation by the IDSA states that all orthopaedic surgery tissue and fluid specimens sent for culture following intraoperative collection should be processed promptly after transport inside sterile containers and the processing time should not exceed a two-hour window [1]. This is of the utmost importance in limiting the time frame in which the microorganism is without nutrients and in an uninhabitable environment.

The aforementioned IDSA guidelines outline how delicate the lifecycle of prokaryotic and simple eukaryotic organisms can be

and how at any time during the specimen collection, transport and processing progression, it can be disrupted or altered leading to misinterpretation of the final result [1]. Incorrect interpretations of the final result, whether by subjective human nature, automated analyses or unwanted contamination, can and will have major implications in the management of patients in which these specimens originated.

In an effort to maintain the same level of certainty in the detection of PJI for revision total joint arthroplasty (TJA) cases, it has been recommended that a minimum of three specimens for culture be taken intraoperatively [1,2]. A prospective study by Atkins et al. examined 297 revision TJA procedures using multiple detection methods included in a mathematical algorithm to determine each diagnostic test's performance in identifying cases with infection [3]. They recommended that there should be five to six specimens collected from revision arthroplasty procedures in order to properly diagnose an underlying infection and at the very minimum, at least three specimens collected should yield growth of the underlying microorganism for adequate diagnosis of infection [3]. They further recommended labs should abstain from using Gram staining as a clinical diagnostic tool.

Studies have shown that there is much needed research in determining how the eventual use of implant sonication, blood culture bottles and other novel molecular techniques once brought into standard practice may further the capability of diagnosing orthopaedic surgery associated infections [4–6].

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QUESTION 5: Does preoperative swabbing of a sinus tract have a role in the isolation of the infecting organism?

RECOMMENDATION: Superficial cultures obtained from a sinus tract should be discouraged in the setting of an infected arthroplasty. Cultures from superficial swabbing of a sinus tract exhibit a low rate of concordance with deep cultures, thus, the value of obtaining such cultures is limited. Furthermore, these cultures can confound the decision-making process in the management of periprosthetic joint infection (PJI).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 96%, Disagree: 3%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Patients may develop a draining wound in the early postoperative period following hip and knee arthroplasty or a sinus tract in the setting of a chronic PJI. Oftentimes, cultures are obtained from these superficial areas in an attempt to either diagnose a deep infection or identify the infecting microorganisms. The Musculoskeletal Infection Society (MSIS) definition for PJI, and the recent validated definition of PJI introduced in 2018, include the presence of sinus tract communicating with the prosthesis as a major diagnostic criterion for PJI [1,2]. The direct communication of the sinus tract with the epithelial surface of the skin results in contamination of the tract by organisms that may not be the infective agents in causing the underlying PJI. Although culture of the sinus tract and the draining wound is likely to be positive and isolate organism(s), the infecting organisms isolated by such method are not thought to be representative of the underlying PJI.

Historically, the swabbing of the sinus tract most likely derives from clinical practice in the diagnosis and treatment of osteomyelitis, in which it was assumed to accurately identify the causative organism [3]. There is scarce literature regarding to the use of superficial cultures in the diagnosis of PJI [4–6], and previous studies predominantly deal with sinus tract sampling in the setting of chronic osteomyelitis [7,8].

In 2013, the International Consensus Meeting (ICM) on PJI recommended against taking wound swab cultures [9]. Tetreault et al. [4], in a prospective, multicenter study evaluated the utility of culturing draining wounds or sinus tracts following hip or knee arthroplasty. This study included 55 patients, and reported that superficial cultures were concordant with deep cultures in less than half of the cohort (47.3%) and were more likely to generate polymicrobial results (27.3% versus 10.9%, $p = 0.023$). In 23 cases (41.8%), the superficial cultures would have led to a change in antibiotic regimen. Furthermore, in 8 of 10 patients the sinus swab yielded a positive result for an organism which was not supported by other tests. The authors concluded that obtaining superficial cultures of the sinus tract should be discouraged in the setting of a hip or knee arthroplasty. These results were consistent with prior studies in chronic osteomyelitis [7,8], which also demonstrated low correlation between sinus tract and bone cultures.

Similarly, Aggarwal et al. [6], in another prospective study, demonstrated that swab cultures are not as effective as tissue cultures

for diagnosis of PJI. They had more false-negative and false-positive results than tissue cultures, leading to an increased risk of not identifying or incorrectly identifying the infecting organisms in PJI.

Based on the available evidence, it can be surmised that sinus tract swabs do not have a role in the isolation of the infecting organism in patients with underlying PJI.

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QUESTION 6: How should synovial fluid samples be sent (via laboratory vacuum tube, syringe, blood culture tubes, etc.) for culture to increase the culture yield?

RECOMMENDATION: The Infectious Disease Society of America (IDSA) recommends that synovial fluid specimens for culture be transported at room temperature in sterile containers and when ample amounts are available, additional procurement should be made in blood culture bottles (aerobic, and anaerobic if enough specimen volume exists to do so) alongside traditional culture methods in an effort to increase culture yield.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 97%, Disagree: 1%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

For centuries, the gold standard in the identification of disease-causing microorganisms has been microbiological culture. The culture techniques described by Koch in the 19th century has undergone little to no changes. There are numerous issues associated with culture. One of the major issues relates to maintaining the viability of organisms for proper growth and identification during the process of transport [1]. Clinical microbiological laboratories have well-defined methodologies in place to maximize culture yield in an effort to better serve and manage patients who are at risk for developing surgical site infections (SSI) and periprosthetic joint infections (PJI). There is limited evidence to show what the optimal method of transport (i.e., container and movement) allows for the highest culture yield possible. No studies have outlined the differences between transport via hospital personnel versus automated vacuum tube transport and its effects on culture yield.

Despite the limited evidence, the IDSA recommends that PJI synovial fluid samples be procured at room temperature in a sterile container that is to be processed and incubated within a two-hour window for optimal culture results [2]. They also suggest that when there is abundant specimen, an additional 10 mL be transferred aseptically into an aerobic blood culture bottle and processed using blood culture study methods. Studies have shown that the blood culture broth may allow for the dilution of host immune cells including inflammatory factors and polymorphonuclear leukocytes which may permit subsequent growth of organisms not obtained by traditional culture [3,4]. Evidence does show that using blood culture bottles for synovial fluid from patients with suspected septic arthritis enhances the yield of pathogenic bacteria, albeit at a small cost of increased isolation of contaminants [5]. A study by Peel et al. found that in using blood culture bottles for collection of periprosthetic tissue samples they were able to drastically increase detection rates of underlying infection [5]. Other methods in the procurement process have been attempted in order to increase the sensitivity and detection rate in the overall culture process. A study by Sebastian et al. found that sonication of implants and fluid improved the culture's diagnostic sensitivity for PJI [6]. However, this is post-transport and post-procurement which was done in standardized sterile transport containers. There is a current void in research regarding the optimal method for synovial fluid specimen transport and further research is needed in an effort to determine methodologies capable of producing the highest culture yield.

In the absence of data we recommend that the guidelines of the IDSA regarding culture procurement be followed. Culture samples taken during orthopaedic procedures should be collected using sterile instruments, transferred directly into sterile bottles and transported to the laboratory as soon as possible. The cultures may be transferred at room temperature. Culture yield will be increased by transporting and processing synovial fluid in one or more blood culture bottles albeit with slightly higher bacterial contamination rates. Time to culture medium inoculation and/or loading onto incubation machines should be minimized and a separate ethylenediaminetetraacetic acid (EDTA) or heparin tube for a cell count should be provided with consideration of primary specimen preservation for onward molecular analysis if necessary.

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QUESTION 7: Should perioperative antibiotics be withheld prior to obtaining an intraoperative aspirate and/or tissue samples for culture in suspected infected revision total joint arthroplasty (TJA) cases?

RECOMMENDATION: Administration of perioperative antibiotics during revision arthroplasty should be based on the degree of suspicion for periprosthetic joint infection (PJI) and the results of preoperative culture results. If suspicion for PJI is low or if the infecting organism in a PJI case has been preoperatively identified, then perioperative antibiotics should be administered. In patients with high suspicion for PJI in whom preoperative cultures are negative, perioperative antibiotics should be withheld to improve the yield of intraoperative samples taken for culture.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 81%, Disagree: 16%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Chronic PJI remains one of the most difficult conditions to treat in the field of arthroplasty. Furthermore, when such infections are culture-negative they become even more difficult to treat, as targeted antibiotic therapies are impossible. It has been previously demonstrated that antibiotic administration prior to establishing a causative organism increases the risk of culture-negative infection [1]. However, the need to withhold pre-incision antibiotic prophylaxis remains controversial.

A comprehensive review of the literature identified eight applicable studies that evaluated the impact of perioperative antibiotic prophylaxis on culture yield. Two were randomized clinical trials [2,3], and two more were prospective cohort studies [4,5]. One was a systematic review of the literature [6]. Three were retrospective studies [7–9] with large cohorts of patients who had both pre-and postoperative cultures available for comparison, making both very high-quality retrospective studies.

Overall, the literature overwhelmingly supports giving prophylactic antibiotics at the onset of the case, rather than holding them for cultures to be obtained. The first study to critically examine the issue was a retrospective review of 171 PJI patients [7], all confirmed by a positive preoperative culture. In this study, the authors observed a nearly identical false negative culture for those patients who had received preoperative antibiotics at the onset of the case (12.5%), and those for whom antibiotics were withheld prior to culture (8%) ($p = 0.34$). Furthermore, in all cases, intraoperative cultures isolated the same organism as preoperative cultures. In a follow-up prospective study [5] analyzing a separate patient population, the same group identified 26 infected knee replacements and compared intraoperative cultures following prophylactic antibiotic administration to preoperative aspirations. In all cases, the intraoperative cultures yielded the same organism as the pre-operative aspiration.

Similarly, a randomized clinical trial of 65 confirmed PJI patients [3] demonstrated concordant intraoperative cultures in 82% of patients who received prophylactic antibiotics, compared to 81% in patients for whom antibiotics were withheld. Additionally, a smaller randomized clinical trial [2] found identical rates of positive intraoperative culture between patients who received antibiotics prior to incision and those who did not.

In a prospective study utilizing an intraoperative control, Bedencic et al. [4] took cultures prior to and after administration of antibiotics from the same surgical site and demonstrated no statistical difference in colony forming units (CFUs) between the two sets of cultures. Furthermore, antibiotic concentrations from the surgical bed were above the minimum inhibitory concentration at the time of the second culture. The only false negatives observed were in cases of coagulase-negative *Staphylococcus* and *C. acnes*.

In a recent systematic review of the literature [3,6], pooled results from seven studies demonstrated a statistically significant difference in false-negative cultures if antibiotics were withheld, however a subgroup analysis of chronic PJI failed to reproduce this result.

Most recently, a retrospective review of 425 total knee arthroplasty (TKA) revisions [8] compared culture yield in 114 patients who received preoperative antibiotic prophylaxis versus 284 patients in whom antibiotics were withheld preoperatively. The authors observed no significant difference in culture yields between the two groups ($p = 0.78$). Furthermore, when these patients were classified in accordance with the Musculoskeletal Infection Society (MSIS) diagnostic criteria for PJI, there remained no significant difference in infection rates seen between the two groups (7.1% in the preoperative prophylaxis group vs. 6.7% in the antibiotic withheld group, $p = 0.88$). The authors concluded withholding preoperative prophylaxis to maximize culture yield is likely not as critical as previously thought.

Another recent retrospective review of 110 patients [9] undergoing orthopaedic joint procedures assessed the influence of

antibiotic prophylaxis within 30 to 60 minutes prior to surgery with respect to positive *C. acnes* culture and joint infection [9]. The study categorized patients into two cohorts: infected cases if two or more positive cultures, and contaminated cases if less than two positive cultures, resulting in 64 infected patients and 46 patients with contaminated cultures. While patients in the infected cohort received perioperative prophylaxis more often (72.8% versus 55.8%, $p < 0.001$), no difference was found with respect to time to positive culture regardless of administration of perioperative antibiotics (7.07 days versus 7.11 days, $p = 0.300$). Furthermore, no association was found between administration of perioperative antibiotics and the proportion of sample positivity (71.6% versus 65.9%, $p = 0.390$).

Similar to the previously-mentioned studies, the authors concluded in favor of administration of preoperative antibiotic prophylaxis to protect against surgical site infection.

Overall, the literature supports not withholding pre-incision antibiotics for cases of suspected prosthetic joint infection. It should be noted one common limitation in the aforementioned studies remains the consistency with diagnostic tests (i.e., variable number of intraoperative cultures and no use of sonication). However, given the fact that there is a relatively significant false negative rate of intraoperative cultures, especially in cases of lower virulence organisms, we recommend obtaining preoperative aspiration following an antibiotic holiday to help identify a causative organism prior to revision surgery.

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QUESTION 8: How should divergent results between intraoperative tissue cultures (TCs) and sonication of the prosthesis be managed?

RECOMMENDATION: Evidence on how to address contradictory results between intraoperative TCs and sonication of the prosthesis is still lacking. Current research shows that sonication yields superior sensitivity and specificity over intraoperative TC for the pathogen identification of prosthetic joint infection. There is statistical support for ≥ 5 colony forming units (CFUs) as optimal threshold defining a positive sonicate fluid culture (SFC), however, clinical outcomes and validation are lacking. We recommend that the data be evaluated in light of clinical picture presented.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 86%, Disagree: 6%, Abstain: 8% (Super Majority, Strong Consensus)

SEARCH METHODOLOGY: The literature search was performed utilizing the OVID Medline search database. Search terms included "prosthetic joint infection," "sonication" and "total joint sonication." A total of 134 articles were returned. Abstracts were reviewed and the articles read when necessary to determine inclusion. Exclusion criteria included non-English language, review articles, case reports, non-orthopaedic, non-clinical studies or did not include tissue culture. Thirty-two articles were available for inclusion. These articles were reviewed in entirety, including their bibliography for other potential sources. Eleven of these manuscripts compared SFC to TC and reported on dis-coordinate culture results [1–11].

RATIONALE

A major challenge in the diagnosis and management of periprosthetic joint infections (PJIs) is the accurate identification of the causative organism [12]. Traditional culture methods of synovial fluid, and intraoperative tissue cultures have an unacceptably low sensitivity (0.65) [1,5,12–15]. Most organisms found in PJI reside in a biofilm wherein they are less metabolically active and are surrounded by a protective glycocalyx that shields them from antibiotics and the host immune system [16]. Sonication is a process by which the biofilm is dislodged from the removed prosthesis using ultrasound, permitting these bacteria to be accessible for cultures [1].

SFC has shown consistently superior sensitivity over intraoperative TC in the diagnosis of PJI [1–5,7,9,10]. Trampuz et al. from the Mayo Clinic published one of the earliest and most notable prospective case series utilizing sonication for the diagnosis of PJI [1]. They reported on 331 patients, both aseptic ($n = 253$) and septic ($n = 79$) failures and compared synovial fluid, tissue and sonicate fluid culture.

The sensitivity and specificity of SFC was 78.5% and 98.8% respectively and was significantly greater than that of synovial fluid (56.3% and 99.2%) and tissue (60.8% and 98.1%). Recently Rothenberg et al. published a study on 503 sonicate cultures and found a sensitivity of 97.0% and specificity of 90.0% while TC was 70.0% and 97.0% [9]. Two meta-analyses have been published regarding sonication and the diagnosis of PJI [17,18]. Zhai published the first in 2013 and reported a pooled sensitivity of 80% and specificity of 95% [17]. Liu, in 2017, corroborated these results, and with additional studies included, reported a sensitivity of 79% and specificity of 95% [18]. In addition SFCs increase the isolation of pathogens when antibiotic therapy is stopped within two weeks from surgery [1].

As with any microbiological process, sonication has the potential for contamination producing false-positive culture results [5,13,19]. Therefore, an essential designation when analyzing SFC results is defining what qualifies as a positive culture. Sonicate cultures are often quantified using CFUs. Trampuz recommends ≥ 5 CFU as a cutoff for positivity to optimize specificity and limit false positive results [1]. Rothenberg et al. analyzed their results of 503 sonicated prostheses and independently determined ≥ 5 CFU is the optimal threshold for diagnosing infection with a sensitivity of 0.97 and specificity of 0.90 [9]. Other published studies have reported cutoff values of 1, 3, 5, 20 and 50 CFU but omit the statistical method by which the cutoff was determined [2,10,14,20–22]. In the meta-analysis published by Zhai, the authors reported the optimal cutoff is ≥ 5 CFU [17].

Trampuz identified 14 of 79 (18%) patients with PJIs that had positive SFC but negative TC [1]. Holika et al. found that the bacteria species cultured differed between SFC and TC in six cases [2]. Portillo reported that SFC detected significantly more pathogens than TC (62 vs. 45, $p < 0.001$) as well as more cases of PJI than TC (56 vs. 41, $p < 0.01$) [6]. Other studies have reported greater bacterial isolation in SFC as compared to TC [3,7,8,10,11]. There was no clinical intervention or follow-up reported in any of these studies. A recent study published by Rothenberg et al. reported results of 503 revision procedures with two-year follow-up [9]. Three hundred twenty-five of these patients were presumed aseptic at the time of surgery based on Musculoskeletal Infection Society (MSIS) criteria (53 of 325 had positive SFC and negative tissue culture postoperatively, and 24 had ≥ 5 CFUs/plate). Ultimately 18 of 53 (34%) were treated with antibiotics as the discretion of the treating surgeon and infectious disease team. At the average follow-up of 22 months, only 4 of 53 patients (7%) required surgical intervention. Only 3 of 24 patients (13%) with ≥ 5 CFU required reoperation. Further study is needed to clinically validate the recommendation of ≥ 5 CFU as a true infection.

Although several studies exist that support sonication as a superior method for microbiological diagnosis over tissue culture there are several limitations. First, studies prior to publication of the Musculoskeletal Infection Society definition of infection used a more abbreviated system that may have misdiagnosed patients as not infected [23]. Additionally, the number of tissue samples collected varied widely between studies from two to nine per case [2,3,10]. Lastly, in regard to sonication, studies differed in reporting CFU cutoff for positive culture results and lack of clinical correlation. These inconsistencies influence the reported sensitivity and specificity within this report and limit the strength of recommendation. Further studies with clinical outcomes and validity are warranted.

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QUESTION 9: Is there a role for routine acid-fast bacilli (AFB) and fungal testing in suspected surgical site infection/periprosthetic joint infection (SSI/PJI) cases?

RECOMMENDATION: No. Testing for AFB and fungi should not be performed routinely in suspected SSI/PJI. Testing of suspected cases of SSI/PJI should be limited to only those patients at higher risk of atypical infections which include the following: (A) immunocompromised host, (B) previous history of atypical infection, (C) patient is living in an area with endemic atypical infections and (D) culture-negative PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 6%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

PJI caused by mycobacteria and fungi is very rare [1,2]. In an international multicenter study, the rate of mycobacterial and fungal PJI was reported to be 0.3% and 1.2%, respectively [3]. The practice of routine culture for AFB and fungus in suspected cases of SSI/PJI increases cost to individual patients and the healthcare system [4,5]. Therefore, it has been suggested that only patients with a higher than usual likelihood should be evaluated for atypical pathogens [6,7].

Patients who have PJI and their surgery findings include gross appearance or histological findings suggestive of granulomata disease should have culture samples evaluated for atypical infections. Evaluation of culture samples for atypical pathogens may also be performed if after seven days the culture is negative for any pathogen in the case of a PJI. In this regard, Wadey et al. described an approach to be used during surgeries wherein parts of tissue from each routine culture sample are saved, but not cultured for seven days after surgery. Then, if concerns about a possible atypical pathogen appear postoperatively or after surgical pathology is available, mycobacterial cultures and fungal cultures can be performed using the stored specimens [4]. The delay in culturing would need to be approved as microbiologically acceptable.

This rationale is subject to change as the occurrence of mycobacterial and fungal prosthetic joint infections may become more prominent. Just as *Mycobacterium avium* intracellulare musculoskeletal infection emerged as a prominent problem with onset of the acquired immune deficiency syndrome (AIDS) epidemic, re-activation of endemic dimorphic fungal infections could become a major problem as anti-tumor necrosis factor therapy continues to broaden its spectrum of effectiveness.

The literature review provided no high-quality studies on routine testing of fungal and AFB in suspected SSI/PJI. On the basis of the available literature [1,4,6,8], we recommend selective AFB and fungal cultures in suspected SSI/PJI cases only in the following circumstances: (A) immunocompromised host, (B) previous history of atypical infection, (C) patient is living in an area with endemic atypical infections and (D) culture-negative PJI.

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2.4. DIAGNOSIS: PATHOGEN ISOLATION

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QUESTION 1: Is there a method to detect sessile microorganisms that have resulted in an infection following orthopaedic procedures?

RECOMMENDATION: Yes. Molecular techniques such as polymerase chain reaction (PCR), next-generation sequencing (NGS) and synovial biomarkers such as alpha-defensin or leukocyte esterase have been shown to be powerful tools in detecting prosthetic joint infections (PJI) with negative cultures, although conflicting data exists on PCR. Sonication of explanted prosthetics can enhance both the sensitivity of conventional cultures and PCR.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree:85%, Disagree: 9%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

The colonization of prostheses by sessile bacteria is a feared complication of orthopaedic procedures. These microorganisms anchor themselves to the surface of prosthetic implants and form a colony of immobile bacteria cross-linked by an extracellular matrix of polymeric substances, known as biofilm [1]. The presence of biofilm on prosthetic implants, especially that of prosthetic joints, makes both detection and treatment of infections difficult [2]. While there is no gold standard for definitive diagnosis of PJI, a multi-criteria definition created by Musculoskeletal Infection Society (MSIS) is often used is to diagnose PJI [3,4]. The MSIS criteria utilizes the obtaining of cultures of joint aspirate or periprosthetic tissue as one of the major criteria to prove the presence of pathogens in the prosthetic joint. Unfortunately, cultures can be unreliable when detecting biofilms [5,6]. Intraoperative cultures alone also can have a high rate of contamination and false positives [7]. Thus, alternative methods of confirming the presence of organisms in PJI have been proposed [8,9]. Some of these diagnostic techniques include PCR, NGS, prosthesis sonication and joint biomarkers.

Polymerase Chain Reaction

The use of PCRs to detect bacterial nucleic acids in prosthesis infections can be an effective way of detecting sessile microorganisms otherwise not picked up in cultures [10,11]. PCR sequencing of bacterial ribosomal nucleic acids has shown to have higher sensitivity in detecting bacteria than culture, as well as identifying polymicrobial infections that may not be picked up by culture [12–15]. Jahoda et al. showed that the use of PCR can detect as few as 590 colony forming units of *S. aureus*, making detection of PJI even in the presence of antibiotics feasible [11]. PCR has also shown benefit in detecting genes responsible for biofilm production and methicillin resistance [11,16].

In spite of the literature describing the merits of PCR, there is data suggesting that the efficacy of PCR is not as high as once thought. Studies have suggested that PCR has similar or less sensitivity for detecting bacteria in PJI as traditional cultures [17–20]. PCR has also been shown to have questionable sensitivity over the last years. A meta-analysis performed by Jun et al. looking at online databases from 2013 to 2017 showed that there has been a decrease in pooled sensitivity compared to a previous meta-analysis performed by Qu et al. in 2013 (0.76, (95% confidence interval (CI) 0.65-0.85) vs.0.86, (95% CI 0.77-0.92) respectively), with no change in specificity [21,22].

Next-Generation Sequencing

Recently, NGS has proven to be efficacious in diagnosis of culture-negative PJIs as well. A prospective study performed by Tarabichi et al. evaluated the accuracy of NGS in identifying PJIs in 78 patients undergoing revision or primary arthroplasties. NGS identified infections in 25 of the 28 cases considered to be PJIs by MSIS criteria (95% CI 71.8% to 97.7%), whereas cultures were only able to identify 17 cases (95% CI 40.6% to 78.5%). In cases where both cultures and NGS were positive, NGS showed a high degree of concordance to traditional cultures as well [23].

NGS has also shown high degrees of detection in synovial fluid samples. Another study conducted by Tarabichi et al. analyzed 86 samples of synovial fluid from the hip or knees of patients undergoing PJI evaluation. They found that NGS had a positive result in 10 samples that were culture-negative. Five of these samples had elevated inflammatory biomarkers, indicating an infectious process, while the other five had negative inflammatory biomarkers. These results suggest that NGS may be a valuable tool for evaluating for PJIs in the preoperative setting, but may also be at risk for false positives [24].

In addition to diagnosing prosthetic infections, NGS may also be useful for identification of causative organisms in culture-negative PJIs [23]. Furthermore, the speed at which NGS can explore an entire genome makes it a superior alternative to PCR [25]. While NGS has exciting potential as a powerful diagnostic tool for culture-negative PJIs, there has been limited data showing its effectiveness in diagnosing other prosthetic infections. In addition, there has been no direct comparison between the effectiveness PCR and NGS. Finally, it is important to consider that the high sensitivity may predispose NGS to a high false-positive rate and false diagnosis of PJIs [25].

Sonication

The use of sonication to break up biofilm in prosthetic implants has been shown to increase the sensitivity of both cultures and PCR when testing for infection. A prospective study performed by Tani et al. compared the sensitivity and specificity of cultures obtained from sonicated explants to conventional cultures of periprosthetic tissue in 114 patients who underwent hip and knee revisions due to PJI and aseptic loosening. Sonicated cultures had a significantly-increased sensitivity when compared to conventional cultures (77.0% vs. 55.7%). There were no significant differences in specificity of either detection method [26].

There are some studies suggesting that sonication of prosthesis may improve the diagnosing capacity of PCR in the diagnosis of culture-negative PJIs [27–29]. However, their statistical significance remains controversial. A recent meta-analysis of nine studies looking at the efficacy of sonication in PCR was performed by Liu et al. [30] found that PCR for sonication prosthetic fluid was to have clinically acceptable diagnostic values for detecting PJIs, with a pooled sensitivity of 75% (95% CI 0.71 to 0.79) and specificity of 96% (95% CI 0.94 to 0.97) [30].

Joint Biomarkers

Inflammatory biomarkers in the blood such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as well as synovial fluid leukocyte esterase have been part of the 2011 MSIS criteria and the 2013 consensus group modification criteria in the diagnosis of PJI [3,31]. The updated MSIS criteria put forth by Parvizi et al. in 2018 added the presence of synovial alpha-defensin and synovial CRP as criteria for diagnosis of PJI [4]. Synovial biomarkers such as leukocyte esterase and alpha-defensin have been shown to have high sensitivity and specificity in diagnosis of PJI, and are more specific than serum inflammatory biomarkers [32–34]. The benefit of these biomarkers are that they are faster and less invasive than traditional cultures. Biomarker assays also do not require tissue sampling and may be performed on synovial fluids, which increases the convenience of these tests in diagnosing PJIs in the preoperative setting. The major drawback of joint biomarkers is that they can only indicate the presence of infection and not its specific nature. Therefore, biomarkers are best utilized as a preliminary indicator of the presence or absence of joint infection. They are best followed up by diagnostic assays such as PCR, NGS or cultures to better determine the nature of infection.

Conclusion

There are a number of methods to detect sessile microorganisms in infections following orthopaedic procedures. The use of PCR in the diagnosis of culture-negative PJI has shown to be more sensitive than traditional cultures but there is conflicting data. The use of inflammatory biomarkers in both the blood in synovial fluid is also effective, but cannot characterize the nature of infection or organism involved. NGS is a new test can determine the presence of sessile microorganisms with more precision and speed than traditional cultures. Finally, sonication of explants has shown to improve the sensitivity of both cultures and PCR in diagnosing prosthesis infections.

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QUESTION 2: What is the preferred type of sample (tissue, fluid, etc.) for molecular analysis in the diagnosis of orthopaedic infections?

RECOMMENDATION: Several molecular methods have been developed in an effort to provide a viable culture-independent alternative for diagnosis of orthopaedic infections. However, due to the variation between studies with respect to the techniques and variety of samples collected, it remains difficult to recommend collection of one specimen type over another. While we cannot recommend a single molecular diagnostic test, careful assessment of the individual technique (location, volume, medium, temperature and transport) utilized is needed for appropriate collection and yield from the corresponding samples.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 87%, Disagree: 2%, Abstain: 11% (Super Majority, Strong Consensus)

RATIONALE

Identification of the infecting organism is imperative in the management of periprosthetic joint infection (PJI) [1,2]. Unfortunately, current methods, namely culture, have failed to perform at a level where the infecting organism is routinely identified, with up to half of PJIs yielding no known pathogen on microbiological culture [3–7]. Several molecular techniques have been examined to address this issue, however, no single technique has established itself to be superior to others. Furthermore, the optimal specimen type for maximizing the sensitivity and specificity of such technologies is an even greater dilemma.

Conventional cultures typically rely on synovial fluid from aspiration, when available, as well as multiple tissue samples obtained intraoperatively. Swabs have largely fallen out of favor with evidence demonstrating their lack of sensitivity and specificity [8]. Culture of sonicate fluid has shown some promise, however conflicting results and the need for specialized equipment preclude its routine use [9].

Synovial Fluid

Synovial fluid has been studied extensively as a source material for identifying the infective organism in PJI. When successfully obtained in the preoperative setting, it may provide the surgeon with crucial information to help guide further operative management of a patient with PJI. Various studies have reported on the performance of synovial fluid based molecular diagnostics in isolation or in parallel with other specimen types. In a study by Huan et al., samples of periprosthetic tissue, sonication fluid and synovial fluid were collected for both culture and 16S broad-range polymerase chain reaction (PCR). The authors concluded that PCR of sonication fluid and synovial fluid were significantly more sensitive than PCR of periprosthetic tissue alone, with no difference in specificity [10]. Multiple studies have shown superiority of synovial fluid PCR to conventional culture, however, these studies simply assessed synovial fluid with no direct comparison to other specimen types [4,11–13]. In contrast, a study comparing the combined sensitivity and specificity of joint fluid culture and serum C-reactive protein levels versus synovial fluid PCR demonstrated inferior results.

Periprosthetic Tissue

Periprosthetic tissue is a useful specimen due to its abundance, as opposed to synovial fluid which may only be present in limited quantities, if at all. A meta-analysis by Qu et al. comparing tissue, synovial fluid and sonication fluid concluded that tissue samples conferred the maximal sensitivity, while sonication fluid helped optimize specificity [14]. Other reports have claimed that tissue PCR is inferior to culture, however these studies focused on a comparison between sonicate fluid culture/PCR and tissue [15,16].

Swab

Swabs have been used in a limited fashion for molecular analysis. Omar et al. compared swabs sampled for 16S rRNA PCR with those sent for tissue culture, and showed a higher sensitivity in favor of swab PCR compared to culture. This is the only report assessing the utility of swabs for molecular diagnosis of PJI. However, no direct comparison was made to other specimen types in this study [17].

While 16S rRNA PCR forms the bulk of studies assessing the different specimen types, there are emerging reports of newer techniques such as next-generation sequencing that will also need to be further explored in order to delineate the optimal specimen type [18–20]. Emerging evidence suggests that the use of gauze or larger swabs that are able to potentially sample a greater intraoperative surface area may confer a better sequencing yield.

In conclusion, the optimal specimen type for molecular analysis of PJI remains unknown. There is significant heterogeneity between studies with regard to the techniques assessed as well as the samples analyzed. Careful assessment of specific techniques are advised when using these technologies as part of the diagnostic workup.

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QUESTION 3: What is the best diagnostic method for identifying a *C. acnes* surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Microbiological cultures, incubated for a prolonged period (up to 14 days) is currently regarded as the best diagnostic method for identifying *C. acnes*. Subculture in thioglycolate broth is believed to improve the yield of culture for *C. acnes*.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 3%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

C. acnes is a slow-growing, anaerobic, aerotolerant, non-sporulating, gram-positive bacillus [1]. It is part of the normal microbiome of the skin and resides in deeper layers [2]. The strains isolated in cases of invasive infections (especially in relation to orthopaedic implants) differ from those identified on the skin surface in their capacity to produce biofilms [3,4]. Diagnosing low-grade infection after total joint arthroplasty (TJA) is often highly complex, as clinical symptomatology and diagnostic studies may conflict [5,6]. *C. acnes* is also a common contaminant of bacterial cultures, thus the significance of recovering this organism from periprosthetic specimens is not always clear [7].

Clinical Signs and Symptoms

Diagnosis of hip and knee PJI caused by *C. acnes* remains challenging. This is primarily due to its indolent nature, which results in pain and stiffness as major complaints, rather than in the more classic signs of infection [6–9].

Serum Biomarkers

Tebruegge et al. found that white blood cell (WBC) count was normal in 75% of orthopaedic *C. acnes* infections [10] and several studies indicate that serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have a low sensitivity in such low-grade infections [5,7,10–14]. In a study focused on *C. acnes* total knee arthroplasty (TKA) infections [8], Nodzo et al. found that ESR and CRP levels were statistically lower in the *C. acnes* PJI group, as compared to a *Staphylococcus aureus* TKA infections (ESR: 23 mm per hour vs. 56 mm per hour, CRP: 2.0 mg/dl vs. 5.9 mg/dl). In a prospective study by Grosso et al. [15] on 69 patients who underwent revision shoulder arthroplasty, serum IL-6 was not an effective marker for diagnosing infection.

Synovial Biomarkers

Synovial fluid leukocyte count and neutrophil percentage have been reported as having high sensitivity and specificity in diagnosing

hip and knee PJI [16–18]. The utility of the proposed cutoff points in cases of low-grade infections is unknown [13,19]. In a recent study by Nodzo et al., comparing 16 TKAs due to *C. acnes* PJI to 30 *S. aureus* TKA infections [8], the authors found that the median synovial fluid WBC count in the *C. acnes* group was 19,950 cell/mm^3. This was similar to the count in their *S. aureus* group (26,250 cell/mm^3, p = 0.31), as was the median percentage of polymorphonuclear cells (PMNs) in the synovial fluid (95.5% vs. 95%, respectively, p = 0. 13).

With regard to synovial IL-6, a recent investigation found a strong association between elevated synovial fluid IL-6 level and positive *C. acnes* culture [20] in cases of shoulder PJI.

The presence of leukocyte esterase (LE) in the synovial fluid has recently been proposed as a quick and effective marker for PJI [21]. Its utility in cases of low-grade infection has not been fully investigated. In a prospective study focused on shoulder arthroplasty, the sensitivity of LE was 30% and the specificity was 67%. *C. acnes* was isolated in 63% of all positive cultures.

Numerous studies posit alpha-defensin 1 (AD-1) as a valuable biomarker for diagnosis of PJI [22–25]. Although alpha-defensin has been proven useful regardless of organism type [26], its utility in cases of low-grade pathogens like *C. acnes* is a matter of debate. In a recent prospective study by Frangiamore et al., 33 cases of painful shoulder arthroplasty were evaluated for infection [27]. They found that alpha-defensin showed a sensitivity of 63%, a specificity of 95% and an area under the curve (AUC) of 0.78 for diagnosis of shoulder PJI. Although 63% sensitivity is not ideal for detecting all infections among infected cases, they found this an improvement over other preoperative tests. They also found a strong association between α-defensin levels and the growth of *C. acnes,* compared with a negative culture growth. The risk of having an α-defensin false-negative result [28] must be taken into account in such low-grade infections, along with the fact that the alpha-defensin test does not provide information on the identity of the infectious pathogen.

In summary, the utility of serum and synovial markers in the diagnosis of *C. acnes* periprosthetic joint infection remains unclear and in need of improvement.

Culture Techniques

C. acnes is a slow-growing, fastidious bacteria, which necessitates a longer incubation period than those routinely allowed for orthopaedic specimens. For a long time, *C. acnes* was underdiagnosed in bone and joint infections due to the short cultivation times routinely used in diagnostic laboratories [29–31]. In a study [8] comparing *C. acnes* TKA infections (16 cases) and *S. aureus* TKA infections (30 cases) the meantime for culture growth in the *C. acnes* group was 8.3 ± 2.0 days, whereas it took a mean of 1.8 ± 0.8 days for *S. aureus* cultures to produce results (p < 0.0001). In another study, *C. acnes* cultures became positive at 3 to 27 days after surgery (45% of cultures were positive at 1 week, 86% at 2 weeks, 97% were positive at 3 weeks and 100% were positive at 4 weeks), so false-negative cultures for *C. acnes* may be as a result of short incubation or inadequate number of culture samples [11]. On the other hand, prolonging the incubation beyond a point (for instance beyond 14 days) may result in a high percentage of false-positive culture results, as *C. acnes* is a common contaminant of culture in microbiology laboratories.

It is common knowledge that *C. acnes* requires more than five incubation days to grow if routine cultures are used [32], but the best appropriate cultivation time is a point of controversy within the scientific community. Recent studies recommend a prolonged cultivation time – up to 14 days [31,33] – however, prolonging the incubation period is costly and labor-intensive and could also increase the likelihood of detecting organisms that are not clinically relevant. A recent study suggested that seven days of incubation should be sufficient for accurately diagnosing orthopaedic implant-associated infections [34]. In this study, 96.6% of the infections were detected within 7 days, however *C. acnes* caused only 1 out of the 58 infections studied. However, a study by Bossard et al. [30], focusing on 70 patients with *C. acnes* orthopaedic infections, found that reducing cultivation time to 7 days resulted in misdiagnosis in 15 patients (21.4%). Furthermore, the study showed that prolonging cultivation time beyond 10 days did not improve sensitivity. Thus, the authors recommend 10-day cultivation followed by a blind subculture in thioglycolate broth, in cases where suspicion of *C. acnes* infection is high. They found that thioglycolate broth culture of tissue biopsy specimens showed a significant difference in median time to positivity (p = 0.0001) as compared to other methods. Thioglycolate broth was most effective for the isolation *C. acnes* (sensitivity 66.3% in tissue samples and 75% in bone samples) with significantly different results than those for aerobic and anaerobic agar plates (sensitivity, 5.1% and 42.1%, respectively, p = 0.0001).

Culture for 10 days to isolate *C. acnes* is also supported by another study by Frangiamore et al. [35] evaluating shoulder arthroplasty patients. In a very recent study by Rieber et al., anaerobe culture became detectable in supplemented liver thioglycolate broth within six days, emphasizing the importance of using supplemented growth media to enhance detection of these pathogens [14].

There is a concern that longer incubation periods have the potential to yield false positive results due to specimen contamination, and may not be helpful for identifying true infections. In a study by Bossard et al., 61.7% of samples belonging to their no-infection group were recorded after day 7. These results are consistent with another study by Butler-Wu et al., which showed 21.7% of cases in which only 1 positive *C. acnes* sample labeled as no-infection became positive after day 13 [31]. The proportion of positive cultures and the timing of culture growth may help to distinguish a true-positive from a false-positive result. In a retrospective study of 46 shoulder arthroplasty revision cases in which a positive *C. acnes* culture was identified, the time to culture growth was significantly shorter in the probable true-positive culture group (p = 0.002) compared with the probable contaminant group (median 5 days vs. 9 days). Significantly fewer days to culture growth were demonstrated among cases with a higher number of positive cultures (p = 0.001) and a higher proportion of positive cultures [35]. PJI specimens (true positives) were 6.3-times more likely to have 2 culture media positive for *C. acnes* growth than specimens from non-diagnostic events, and the authors considered a single culture-positive specimen in the absence of histologic findings to be non-diagnostic and most likely representing contamination [5,31].

Recent studies have suggested an improved effectiveness of the implant sonicate fluid culturing method over conventional periprosthetic tissue culture in detecting bacteria in total knee and total hip arthroplasty patients because of its ability to disrupt biofilm membranes [36]. Such superiority in cases of *C. acnes* infection is a matter of debate. A study conducted by Piper et al. [37], investigating the utility of implant sonication in 136 cases undergoing shoulder arthroplasty or resection, found that sonicate fluid culture was more sensitive than periprosthetic tissue culture for detection of definite prosthetic shoulder infection (66.7% vs. 54.5%, respectively, p = 0.046). A recent study by Portillo et al., investigating the sensitivity of sonication in 39 orthopaedic implant-associated infections – including 5 cases with *C. acnes* infection – detected all 5 *C. acnes* infections by sonication, but only 2 by conventional tissue cultures [38]. However, other authors have not found such advantages to the use of sonication in cases of *C. acnes* PJI. In a recent study by Bossard et al., which investigated the optimum cultivation time for isolation of *C. acnes* [30], sub-analysis of 35 cases with PJI caused by *C. acnes* found a 96.2% sensitivity for tissue biopsy specimens (25/26 cases) with at

least 1 positive culture, as compared with sonication fluid at 46.2% (12/26). Grosso et al. evaluated the utility of implant sonication fluid cultures in diagnosing periprosthetic joint infection as compared with standard culture techniques in patients undergoing revision shoulder arthroplasty [39]. They found that implant sonication fluid cultures showed no significant superiority to standard intraoperative tissue and fluid cultures in the diagnosis of infection in patients undergoing revision shoulder arthroplasty.

Molecular Techniques

In recent years, several molecular tests that can detect the presence of pathogens by evaluating the genetic trace of these microorganisms have become available [40,41]. Such tests seem very promising, but they are also a target of ongoing criticism. One significant challenge for polymerase chain reaction (PCR) test is its inability to distinguish clinically important infections from mere traces of dead bacteria or bacteria that are part of the normal microbiota. Culture-independent techniques as species-specific PCR or broad-range16S rDNA PCR have been used in the diagnosis of PJI. The high sensitivity in the detection of bacterial DNA and non-viable forms (useful in case of previous antimicrobial treatment) are described among its advantages [6,42,43]. In a recent study by Morgenstern et al., synovial fluid multiplex PCR was found superior to synovial fluid culture for detection of low-virulence bacteria such as *C. acnes* and coagulase-negative staphylococci [44]. Holmes et al. [41], developed a PCR-restriction fragment length polymorphism (RFLP) approach that identifies *C. acnes* in tissue specimens within a 24-hour period. This PCR-RFLP assay combines the sensitivity of PCR with the specificity of RFLP mapping to identify *C. acnes* in surgical isolates. The assay is robust and rapid and a *C. acnes*-positive tissue specimen can be confirmed within 24 hours of sampling, facilitating treatment decision making, targeted antibiotic therapy and monitoring to minimize implant failure and revision surgery [45].

However, they are not exempt from limitations. The limit of detection of the target sequence can be variable for each test, and in the absence of a quantitative technique, it can be difficult to determine whether a positive signal represents contamination or a clinically relevant infection. [6,42,43]. The universal PCR has difficulties in the case of polymicrobial infections and a low sensitivity for the diagnosis of PJI has been described [45,46].

The utility of molecular techniques, although promising, remains to be explored in the setting of *C. acnes* implant-associated infections [41,47]. Another new molecular technique that is gaining popularity is the use of next-generation sequencing (NGS) for identification of infecting pathogens causing PJI [48]. Based on a recent study from the Rothman Institute, NGS appeared to have a promising role in the identification of infecting organisms in over 80% of culture negative cases that included isolation of *C. acnes* in some cases. An ongoing study examining patients with shoulder pathophysiology at the same institution appears to indicate that NGS may be a better test than traditional culture for isolation of slow-growing organisms, such as *C. acnes* that result in PJI (data to be published soon).

Histologic Analysis

Frozen section histology of periprosthetic tissues has been recommended for patients undergoing revision hip or knee arthroplasty, for whom a diagnosis of PJI has not been established or has not been excluded [49]. There is a concern that low-virulence organisms like *C. acnes* could induce a less vigorous inflammatory reaction, characterized by a lower tissue concentration of neutrophils. According to data from a study by Grosso et al., frozen sections show a low sensitivity [50] in shoulder *C. acnes* infections (50%) using the diagnostic thresholds currently recommended for revision hip and knee arthroplasty (Feldman's criteria). The authors recommend a threshold of 10 polymorphonuclear leukocytes per 5 high-power fields, which results in an increased sensitivity (73%). In other instances, such as in a comparative study by Nodzo et al. [8], acute inflammation was identified in 88% of available tissue samples (14/16) in the TKA *C. acnes* infection group, as compared to 100% of samples (29/29) in the *S. aureus* group ($p = 0.05$).

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QUESTION 4: Should organisms (e.g., *Treponema spp.*, *Corynebacteria spp.*) identified through molecular or genetic testing be treated the same as the pathogens isolated by culture?

RECOMMENDATION: No. Because of their associated poor clinical outcomes, unusual organisms resulting in infection should not be treated equivalently to a usual pathogenic organism. Identification of unusual organisms through molecular and genetic techniques should help aid in antibiotic selection in conjunction with surgery, as indicated. Because of the associated poor clinical outcomes of unusual organisms and polymicrobial infections, the results of these newer techniques should not be ignored, but instead used to help inform therapeutic choices.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

There are variety of unusual organisms that can cause periprosthetic joint infections (PJI) aside from *Staphylococcus* species. Unusual organisms represent about 4.5% of the PJIs in the United States, while culture-negative infections account for 18.6% [1]. Many of these

uncommon organisms, in addition to the culture-negative organisms, are associated with polymicrobial PJIs [2]. In order to manage such patients, broad-spectrum antibiotics are often required that need tailored to the specific organisms causing the infection due to high rates of antibiotic resistance [2].

In recent a retrospective study, methicillin-resistant *Staphylococcus aureus* (MRSA), Pseudomonas and Proteus-related PJI have been associated with lower infection-free rates, which means more surgery and hospital time are required for definitive treatment [3]. Thus, aside from MRSA, there are other organisms that are associated with poor PJI outcomes.

In polymicrobial PJI, clinical outcomes were reported to be poor when compared to monomicrobial or culture-negative PJI [2]. In addition, polymicrobial PJI had higher rate of amputation (odds ratio (OR): 3.8, 95% confidence interval (CI) 1.34 to 10.80, $p = 0.012$), arthrodesis (OR: 11.06, 95% CI 1.27 to 96.00, $p = 0.029$) and PJI-related mortality (OR: 7.88, 95% CI 1.60 to 38.67, $p = 0.011$) compared with patients with monomicrobial PJI [2]. In such polymicrobial PJI, gram-negative organisms (OR: 6.33, $p < 0.01$), enterococci (OR: 11.36, $p < 0.01$), *Escherichia coli* (OR: 6.55, $p < 0.01$) and atypical organisms (OR: 9.85, $p < 0.01$) isolation were associated with polymicrobial PJIs [2]. PJI due to gram-negative species such as *Pseudomonas aeruginosa, Escherichia coli* and *Klebsiella pneumoniae* have proved to have lower rates of therapeutic success following debridement when compared to gram-positive organisms [4].

Fungal infection should also be recognized as an atypical organism causing PJI. Although the reports describing PJI due to fungal infection are limited, the clinical outcomes of PJI by *Candida* species were unsatisfactory. It was reported that the overall rate of mortality attributable to *Candida* PJI was 25% [5]. Multidrug-resistant gram-negative organisms, such as carbapenemase-producing *Klebsiella pneumoniae,* require aggressive medical and surgical treatment [6]. In a small case series of *Propionibacterium avidum* PJIs, debridement-retention of the prosthesis was not an effective option [7]. Similarly, although *Enterococcal* PJI is not frequent, its successful rate of treatment was reported to be low [8,9].

Because clinical outcomes can be associated with the characteristics of the causative agent, the ideal goal is to properly identify all pathogens responsible for the infection [2]. However, some of these unusual organisms can be difficult to detect or take excessive time to appropriately culture [10]. Negative culture results can pose a challenge for physicians therapeutically, for they lack vital diagnostic information, such as the true identity of the causative agent(s). Recently, research has focused on newer innovative methods of infection detection and identification. At the forefront of these new innovative techniques are molecular and genetic methods such as polymerase chain reaction (PCR) assay. Although current molecular and genetic methods tend to have high sensitivities, their specificities are lower and therefore cannot be used as a single diagnostic test as of now [10]. However, as technologies continue to improve, more insight into the pathologic agents will likely become available allowing physicians to make more informed therapeutic decisions based on information such as the presence of antibiotic resistant genes.

A study by Tarabichi et al. examined the utility of some of the newer molecular and genetic techniques, also known as next-generation sequencing (NGS) [11]. Based on the results of their study, they were able to conclude that NGS may be a useful adjunct to aid in organism identification [11]. Although their study shows much promise, they do note that further larger studies are needed to further validate this new technology.

Although two-stage exchange arthroplasty remains the gold standard for surgical management of chronic PJIs, especially when the causative organism is a resistant microbe or produces biofilm, the emergence of new pathogen identification methods will potentially allow physicians to choose more appropriate antibiotic regimens [9,11,12]. Much research is still needed for further validation of these techniques. However, it is clear that infection secondary to unusual organisms are associated with poor clinical outcomes and therefore should be treated with some variation from standard protocols, even if that is simply a more informed antibiotic regimen choice. Information from newer molecular and genetic techniques shows much promise in aiding in diagnosis of these types of infections.

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2.5. DIAGNOSIS: IMAGING

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QUESTION 1: What imaging modalities are available to help evaluate the extent of an infection and guide bone resection?

RECOMMENDATION: Imaging methods have a potential to demonstrate the extent of soft-tissue/bone involvement in patients with periprosthetic joint infection (PJI). The use of computed tomography, magnetic resonance imaging (MRI) or nuclear medicine techniques may help to delineate the extent of bone and soft tissue involvement and may guide bone resection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 8%, Abstain: 6% (Super Majority, Strong Consensus)

DEFINING THE STRENGTH OF THE RECOMMENDATIONS

Assigning the strength of the recommendations was provided by concise presentation of the literature quantity and quality while accounting for the trade-off between the clinical experience and their limitations. In order to standardize the approach across the consensus document/specialists from different medical branches, we adopted the methodology of defining the strength of the recommendations and evaluating the evidence from the American Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guideline and Systematic Review Methodology v2.0 [1].

The selected studies might be flawed in a number of parameters. For example, study design (randomized-control/prospective/retrospective), type of study (diagnostic/case-control/ observational/case reports), primary purpose, population, study inclusion/exclusion criteria, definition of PJI, gold standard for diagnosis of PJI/distinct clinical entities (abscess, presence of soft-tissue edema, periprosthetic fluid collections, bone damage), data collection/analysis/interpretation etc. Therefore, methods for assigning the quality of the selected studies were appraised in accordance with the GRADE recommendations [2]. In the GRADE approach randomized trials start as high-quality evidence and observational studies as low-quality evidence. Five factors may lead to rating down the quality of evidence: study limitations or risk of bias, inconsistency of results, indirectness of evidence, imprecision and publication bias [3]. In accordance with the AAOS manual [1], high-quality diagnostic studies cannot have any substantial flaw,
moderate-quality studies can have less than two flaws, low-quality diagnostic studies less than three flaws and very low-quality studies have more than three substantial flaws. Observational studies were classified as follows: high-quality studies have less than two flaws, moderate-quality studies have between two and four flaws, low-quality studies from four to six flaws and very low-quality studies have more than six flaws.

RATIONALE

Removal of all infected/necrotic tissues is pivotal in the treatment of PJI. In practice, surgeons are guided mainly by experience of what constitutes infected and/or necrotic tissue that must be excised. Tissue color/structure/consistency can guide the degree of resection, in addition to active bleeding from apparently healthy tissue and bone surfaces. Surgeons may use specific dyes (e.g., methylene blue) as a visual aid to differentiate between necrotic tissue and healthy soft tissue. Currently, there is no consensus on whether imaging modalities could be used preoperatively to better define the location of infected soft tissue and bone or be used to guide the degree and depth of surgical debridement. While imaging methods, such as Indium labeled bone scans, have been used for diagnosis of PJI in very select cases, whether a preoperative imaging modality can provide the spatial resolution and accuracy to determine the exact regions of soft tissue involvement of osteomyelitis that require debridement is still debated [4]. The primary question of this paper is to determine, based on the available evidence, if preoperative imaging, and which type of imaging, could best define the border between the infected and non-infected soft tissue and bone and quantitatively and qualitatively assess the extent of associated soft tissue and osseous damage associated with chronic PJI.

The literature search was conducted utilizing databases such as PubMed, Embase, Cochrane Library, Scopus, ScienceDirect and Google Scholar. The search strategy utilized the following Medical Subjection Headings (MeSH) terms: "hip arthroplasty," "hip replacement," "hip prosthesis," "knee arthroplasty," "knee replacement," "knee prosthesis," "infection," "periprosthetic infection," "prosthetic joint infection," "nuclear imaging," "leukocyte imaging," "antigranulocyte imaging," "18F-fluorodeoxyglucose," "positron emission tomography," "ultrasound," "computed tomography," "magnetic resonance imaging," "conventional radiography" and "best match" for each database.

We used the Boolean operators "AND" and "OR" to identify the intersection and union of the terminology sets. References for all the selected articles were cross-checked.

Two of the authors (EN and LQ) performed the literature search. First, articles were screened by title and abstract; 495 potentially interesting studies were identified. Of them, 229 relevant publications including reviews and meta-analyses were then selected for data extraction.

Study Selection

Based on the clinical question, we proposed inclusion and exclusion criteria to be applied when reviewing the search results of each database. An initial review of titles and abstracts was carried out to identify potential studies. The inclusion criterion was human studies. The exclusion criterion was "studies limited to the English language." This study is based on 49 full texts that have been analyzed to date.

Data Extraction

Once the study selection was completed, the relevant data (number of patients, age, gender, location of PJI, type of PJI, single/multi-center study, study period, type of study, design of study, type of imaging, definition of PJI, gold standard, characteristics of particular imaging methods, limitations of the study) from the included studies were extracted. A spreadsheet was customized to the specific

question. After the data extraction and completion of the tables, the senior authors (JG and MK) assessed the quality of the particular studies used in assigning the strength of the recommendations.

Conventional radiography (CR) can show "signs of damage" in the bone surrounding infected arthroplasty as well as in swollen soft-tissues [5,6]. However, these changes are not specific for PJI, and these are seen only in a minority of PJIs. We did not find any diagnostic study supporting the role of CR in showing the bone/soft-tissue extension of PJI. The conclusion should therefore be *no evidence* for using CR as a tool for visualization of tissues affected by PJI. The only exception is when radiography shows clear presence of osteomyelitis, periosteal reaction and so on and may provide some degree of confidence in planning the extent of bone resection needed during resection arthroplasty.

Ultrasonography can demonstrate collections of fluid inside and around an infected joint as well as it can distinguish between solid and fluid lesions. Sdao et al. reported superficial collections, subcutaneous fistulae, as well as deep periprosthetic collections of fluids around total hip arthroplasty [7]. However, these are not specific for infection. Ultrasound guided aspiration (biopsy) of a hip joint improves reliability of aspiration [8]. Here we suggest concluding the strength of *evidence as low (limited)*. A support for that conclusion is predominantly on anecdotal (case reports) and small-series studies of low quality [9–11].

Computed tomography (CT) is excellent for evaluating bony structures, but it can also contribute to assessment of soft tissue pathology [12]. However, this is not specific for infection. CT can detect abscesses around total joint arthroplasty, which is clinically very useful as a psoas abscess can also mimic PJI [13]. On the other hand, CT arthrography can reveal bone erosions, radiolucency, fistulae, extra-articular extensions of PJI or communications between fluid collections [14,15]. In addition, CT can show displacement of the external iliac vessels with venous compression [11]. Taking these findings into account, alongside the clinical value of CT findings (either positive or negative), we conclude the strength of the recommendations for abdominal/hip CT as *moderate* despite the fact that it is based on anecdotal [16,17] to small-series study evidence [15,18,19]. Therefore, CT should be combined with other imaging/laboratory methods in order to visualize the extension of the soft-tissue/bone damage associated with PJI.

Magnetic resonance imaging (MRI) can detect bone marrow changes, cavities and soft-tissue extension of PJI (edema, fluid collections). In addition, the new metal artifact reduction sequences (MARS) enabled a more reliable assessment of periprosthetic tissues [14]. Contrast MRI can contribute to detection of psoas abscesses [20]. In contrast to radiography, MRI might be more specific for hip PJI as it can differentiate between fluid collections (serous, purulent or hematomas) [21]. Further, progress might lie in optimized MRI parameters with and without view angle tilting (VAT) correction at 1.5 T in coronal fast-spin-echo T2-weighted MRI [22]. Intravenous gadolinium contrast MRI demonstrates improved specificity for abscess detection, despite the fact that non contrast-enhanced MRI with diffusion-weighted imaging has recently achieved comparable performance [23]. Despite that, MRI should be still combined with other imaging/laboratory methods in order to demonstrate the true extension of soft-tissue/bone damage associated with PJI. We suggest concluding the strength of the recommendations for MRI in this specific clinical question as *moderate*, similar to CT.

The nuclear medicine techniques are regularly used in some clinical settings to diagnose particular infections of the musculoskeletal system [24]. They are based on various principles (radio-labelled cells, peptides, antibodies or (18) fluorodeoxyglucose (FDG) to detect patterns highly associated with infected tissues. Recent systematic reviews and meta-analyses show great diagnostic potential in terms of the likelihood ratio for positive/negative results and diagnostic odds ratio for radio-labelled white blood cells [4]. Anti-granulocyte scintigraphy and combined radio-labelled leukocyte and bone marrow scintigraphy appear to be highly-specific imaging modalities in confirming knee PJI. FDG-PET (positron emission tomography) may not be the preferred imaging modality because it is more expensive and not more effective in confirming periprosthetic knee infection [4]. However, much of the evidence is dated and recent innovations in nuclear medicine technology that have improved image quality and sensitivity of investigations (particularly SPECT/CT – single photon emission computed tomography) are not fully represented in this review.

To date, there is a little knowledge of the capability of these methods to visualize the extent of infection across periprosthetic tissues. Radio-labelled leukocyte or antigranulocyte SPECT/CT imaging has been used to differentiate aseptic loosening from infection [4,25].

Filippi and Schillaci [26] described the usefulness of hybrid SPECT/CT in technetium (99mTC)-hexamethylpropleneamineoxime (^{99m}TC-HMPAO)-labelled leukocyte scintigraphy for bone and joint infections. In the sample of 28 consecutive patients (13 of them with suspected orthopaedic implant infection), SPECT/CT differentiated soft-tissue involvement from bone involvement both in patients with osteomyelitis and in patients with orthopaedic implants.

Graute et al. [27] described an added value of the ^{99m}Tc-antigranulocyte SPECT/CT in comparison with SPECT only or planar imaging for detection of low-grade prosthetic joint infections. Joint infections were diagnosed clinically in nine of 31 patients (1 hip and 8 knee prostheses). Hybrid SPECT/CT led to a further increase in sensitivity and specificity to 0.89 and 0.73 (in comparison with 0.89 and 0.45 for SPECT only, and 0.66 and 0.60 for planar imaging, respectively). In the cases presented in this study, SPECT/CT images additionally demonstrated the extent of infection in the bone or bone marrow, revealed infection in patients with a characteristic pattern indicating the presence of synovitis on planar paging, or excluded infection due to physiological uptake in arteria poplitea, etc. Optimal accuracy was obtained through image fusion, which permitted anatomical allocation of foci of pathological tracer accumulation as well as providing information on the extent of infection. By this way this imaging method seems suitable for elimination of both false-positive and false-negative findings.

Trevail et al. [28] similarly described the added value of SPECT/CT for the diagnosis of hip PJI (235 consecutive patients). Imaging comprised Tc-^{99m} bone scintigraphy, Indium-III (In-III) labeled white cell scintigraphy, and bone marrow scintigraphy if required. Similar to previous studies, SPECT/CT allowed more accurate localization of abnormal uptake on bone and white cell scintigraphy. Recently, preliminary results of a study by Liberatore et al. [29] showed potential of white blood cell scan as a guide to open biopsy in the management of hip and knee prosthesis infection.

Tam et al. [30] reviewed the use of SPECT-CT to follow post total hip arthroplasty complications, including aseptic loosening and PJI. The CT component of SPECT/CT may help interpretation of SPECT images. CT may reveal areas of lucency with associated periosteal reaction, which correspond to the increased uptake on scintigraphy. CT can also demonstrate soft-tissues changes, such as joint distension, fluid-filled bursae or collections in muscles.

Also, Palestre et al. [31] suggest the potential impact of SPECT/CT on information about the presence and extent of infection. In patients with positive results, for example, the examination could provide information about the extent of infection as well as other

abnormalities involving the native bone and the prosthesis (joint aspiration and culture could be performed at the same time). In patients with negative results, the CT component could provide information about other causes of prosthetic failure.

In comparison with leukocyte or antigranulocyte imaging, FDG-PET may not be the preferred imaging modality because it is not more effective in confirming periprosthetic infection [25,31]. Periprosthetic activity of FDG can be seen not only during infection but also in synovitis and aseptic loosening [32,33] thus, the specificity of FDG-PET/CT was very low. FDG-labelled leucocyte PET/CT with its high specificity may be a method more useful than labelled leucocyte scintigraphy in periprosthetic infection imaging [34,35]. However, there are some drawbacks to FDG-labelled leukocyte PET/CT including the relatively long time needed for labelling leucocytes, longer time between injection and imaging (three hours), and the necessity of higher injected FDG doses (double the doses used as compared to standard oncological imaging) [35].

Despite lower specificity of FDG described in earlier studies [32,33], a recent retrospective study [36] showed added value of FDG PET/CT in comparison to conventional tests in diagnosing hip PJI (cultures of joint fluid/periprosthetic tissues or clinical follow-up more than six months served as gold standard). Fukui et al. [37] used FDG-PET in order to make more appropriate decision-making in terms of retention of well-fixed uncemented femoral component in two-stage total hip surgery that included delayed reimplantation of an acetabular component in five patients. FDG-PET was employed to assess whether the infection had invaded the bone around femoral component. By a mean follow-up point of 4.2 years after the second-stage operation, none of the 5 patients experienced recurrence of PJI.

Taken together, we suggest concluding the strength of the recommendations for the nuclear medicine techniques in this specific clinical question as *moderate*.

Future Progress

There is an emerging field of new imaging techniques (e.g., molecular imaging methods) that could visualize the extent of infection in musculoskeletal tissues with promising accuracy. However, clinical value of these methods should be demonstrated in well-conducted diagnostic studies.

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QUESTION 2: What are the radiological signs indicative of infection in patients with an arthroplasty component in place?

RECOMMENDATION: The radiographic signs associated with periprosthetic joint infection (PJI) at the site of hip and knee are early loosening, component migration, radiolucent lines and/or bone erosions around the prosthetic components, particularly if seen at less than five years postoperatively. However, it is important to note that plain radiographs are generally normal in the setting of PJI.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Conventional radiography is a simple, safe, relatively inexpensive and clinically valuable method used for routine evaluation of total joint arthroplasty (TJA). However, it is not considered informative enough to contribute to the diagnostic workup in the case of PJI [1]. On the other hand, osteolytic lesions, heterotopic ossifications, loosening and effusion of periprosthetic soft tissues, all being seen on early radiography of TJA, can increase the suspicion of PJI. Other imaging modalities are not thought to have a direct role in the diagnosis of PJI. Artifacts due to the presence of metal are a well-known problem in cross-sectional imaging, especially in magnetic resonance imaging (MRI) [2].

Currently, the attention of the orthopaedic community is focused on data obtained from analysis of joint fluid/periprosthetic tissues/retrieved implants [3,4]. The reason is that removed implants, aspirated joint fluid as well as sampled periprosthetic tissues were in direct contact with invading bacteria at the time of sampling/reoperation. Therefore, data gleaned from these methods are both highly sensitive and specific in relation to PJI, making this diagnosis almost certain or excluding the diagnosis [5]. As a result, imaging methods, with the only exception of specific nuclear medicine studies [6,7], do not contribute significantly to the PJI diagnostic workup due to its high costs, especially at the early stages of infection. However, it does not mean that radiography is of no clinical value.

1. Application of conventional radiography in daily routine.

There is no doubt that conventional radiography is the most common imaging method used in clinical practice for the diagnosis of TJA complications. According to a recent survey, conventional radiography was the most common imaging exam used in patients undergoing investigation for PJI (87.6% of orthopaedic surgeons surveyed) followed by single photon emission computed tomography-computed tomography (SPECT-CT) scans (41.7% of surgeons) [8].

2. Radiographic features associated with PJI.

Importantly, plain radiographs can be normal in appearance in the early stages of infection. The primary radiological signs suspicious of PJI are early loosening, periprosthetic radiolucency and bone erosions (osteolysis) [9]. These features may be present on serial radiographs of patients with either infection or aseptic loosening of the prosthesis [10–12]. Radiographic signs of rapid prosthetic migration (at least 2 mm within 6 to 12 months), rapidly progressive periprosthetic osteolysis and/or irregular periprosthetic osteolysis are highly suspicious of PJI [13,14]. Similarly, bony erosions and new bone formation on plain radiographs occurring within three to six months postoperatively may also suggest PJI [15]. On plain radiographs and computed tomography (CT), diffuse or multifocal osteolysis surrounding the prosthesis (> 2 mm or progressive) raises concern for infection, however this is not always present and can be seen in the setting of aseptic loosening and particle disease too [16].

Inconsistently, there may be other features present, such as scalloping, ectopic ossification, periosteal reaction and sclerosis. A small, very dense bone fragment isolated from the other trabeculae, corresponding to a sequestrum (fragment harboring a pathogen) is highly suggestive of active infection, but this is a rare event (< 8%). The presence of gas around the prosthesis could suggest an infection by an anaerobic organism [17].

Periosteal new bone formation or adjacent soft tissue collection is highly suggestive of infection but are infrequently present. A wide band of radiolucency at the metal-bone interface (or cement-bone interface) with bone destruction could also suggest that infection is present. CT scans rarely may help diagnosis of PJI despite that the presence of a periosteal reaction or soft tissue accumulation near the area of osteolysis, seen on CT scan, is highly suggestive of infection [18].

In a retrospective study [19] of 102 total hip arthroplasties (THAs), 65 stems and 50 cups were loose at the time of surgery, as reported from a set of radiographic findings. The gold standard used to define PJI was culture (which has its own limitations). They found only five stable non-infected stems and three of these had associated radiolucency. Radiolucency of at least 2 mm was seen in 12 of 27 infected loose cups and 4 of 15 infected stable cups. None of the 9 non-infected stable cups had a radiolucent zone reaching 2 mm. Sclerosis was seen in 24 of 65 loose stems, 18 of which were infected (while 6 of 26 uninfected loose stems showed sclerosis also).

In another study [20], radiographs of 20 confirmed infected hip prostheses were examined for the presence or absence of radiolucency, type of lucency (focal or non-focal), rapidity of radiographic change, periostitis, subsidence and cement fracture. No evidence of periprosthetic lucency was seen in 11 of 20 THAs, and focal osteolysis was seen in only 4 patients in the cohort. Most infected THAs showed no abnormal findings at all (10 prostheses together had normal

radiography). The authors concluded that the radiologist should be aware that septic prostheses can appear completely normal.

A retrospective case-control study on 100 total hip replacements assessed the incidence of particular features in the groups of infected THAs, aseptic prosthetic hip failures and successful THAs [21]. The group of failures secondary to infection included 12 of 100 hips. Extensive myositis ossificans was seen in 3 of 12 hips. Resorption of 3 mm in the femoral neck length was noted in 1 hip. Cortical thickening opposite the tip of the stem was seen in one case. Periosteal bone formation was noted in four hips. It involved the proximal part of the femur and usually was circumferential.

In a retrospective case-control study on 41 patients [22], the authors examined which radiographic signs predicted failure of two-stage revision arthroplasty, if present after the first-stage surgery. These radiologic signs were: retained metal implants, new metal implants, retained cement, retained cement restrictor, new fracture, the local antimicrobial delivery system (for example gentamicin loaded beads) and use of a drain. None of these radiographic variables examined was associated with subsequent failure.

A study [23] of 52 patients (32 knees and 20 hips) revised for supposed aseptic loosening and found that there was an association between severity of periprosthetic osteolysis and positive sonication cultures from the retrieved implants (in 30 patients at least 1 sonicated component was positive).

3. Accuracy of conventional radiography for PJI detection.

In a study by Cyteval et al. [24], conventional radiography achieved the following diagnostic characteristics for bone abnormalities (lucency, periostitis): sensitivity 75%, specificity 28%, positive and negative predictive values 19% and 83%, respectively, accuracy 37%. CT images for the same types of findings were similar (75%, 30%, 20%, 84%, 49%, respectively). However, soft tissue abnormalities (joint distension, fluid-filled bursae, fluid collections in muscles and perimuscular fat) were identified on CT as opposed to plain radiography.

In a study by Stumpe et al. [25], serial radiographs had a sensitivity of 84% for the finding of rapid prosthetic migration (at least 2 mm within 6 to 12 months), and/or rapidly progressive periprosthetic osteolysis, and/or irregular periprosthetic osteolysis, whereas specificity was only 57%. In the same study, the inter-observer agreement was very low, limiting the diagnostic value of this technique.

Conclusion

Findings such as early implant loosening, progressive radiolucent lines, early bone erosions (osteolysis) and periosteal reactions (periostitis) can suggest the presence of PJI, especially in the presence of additional supportive clinical data. However, isolated radiographic findings have limited clinical value due to their low specificity.

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QUESTION 3: What is the role of nuclear medicine imaging modalities (three-phase bone scintigraphy, bone marrow scintigraphy, white blood cell (WBC) scintigraphy [with ^{99m}Tc or 111In], anti-granulocyte monoclonal antibody scintigraphy and fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT) scan in diagnosing periprosthetic joint infection (PJI)?

RECOMMENDATION: Nuclear imaging may be used for the diagnosis of hip and knee PJI in a select group of patients. The test may be ordered in patients in whom PJI is suspected but when other tests are inconclusive, such as patients with dry aspiration of the joint.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 85%, Disagree: 10%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The utility of nuclear medicine imaging modalities for diagnosis of PJI has been studied extensively and continues to be debated [1,2]. Two recently published systematic reviews and meta-analysis have evaluated this topic, providing guidance about the utility of nuclear imaging modalities for diagnosis of PJI. Verberne et al. evaluated 31 studies published related to the use of nuclear medicine imaging techniques for the diagnosis of PJI in the hip and found highest accuracy for WBC scintigraphy and highest specificity for combined WBC and bone marrow scintigraphy. FDG-PET and bone scintigraphy were not supported as first imaging technique. FDG-PET showed appropriate accuracy, but its higher costs and limited availability were limitations and bone scintigraphy showed lowest specificity [3]. In a follow-up study, Verberne et al. analyzed 23 publications focused on total knee infections [4]. The authors concluded that antigranulocyte scintigraphy and combined WBC scintigraphy and bone marrow scintigraphy presented the highest specificity values (95% and 93% respectively). In this review (for the knee) bone scintigraphy and FDG-PET/CT were not supported as preferred imaging modality. Bone scintigraphy was not preferred because of low specificity, and FDG-PET/CT was not preferred because of costs and its limited effectiveness in confirming infection for diagnosis of hip and knee PJI.

It is important to realize some facts regarding the nuclear medicine imaging modalities. The three phase bone scan carries a low specificity and low diagnostic accuracy in patients with suspected PJI, particularly in patients with uncemented components and during the early years of arthroplasty [1]. However, the study has a high sensitivity, and normal findings (e.g., no increased perfusion or blood-pool, no periprosthetic uptake in the late phase) can be considered as strong evidence against the presence of infection [5–9]. When having a positive three-phase bone scan in patients with suspected PJI, another imaging modality is necessary. White blood cell scintigraphy is the first nuclear imaging modality of choice in these cases because of the high diagnostic accuracy (> 90%). When correctly labelled, performed and interpreted, FDG-PET/CT has also been used to diagnose PJI. FDG is taken up both in reactive inflammation due to metallic implants such as prosthetic joints and in infection. The differentiation between both is often difficult, leading to lower specificity rates for FDG-PET/CT. Reinartz et al. [10] reviewed the literature on the diagnostic performance of FDG-PET and WBC count scintigraphy in periprosthetic joint infections. They reported higher sensitivity but lower specificity for FDG-PET compared to WBC scintigraphy. In addition, the accuracy for FDG-PET was slightly higher in hip cases than in knee cases. Similarly, a recent review article by Gemmel et al. reported a pooled sensitivity and specificity of 84% for PJI using FDG-PET, which was more accurate for hip than for knee prosthesis [11]. The European Association of Nuclear Medicine/The Society of Nuclear Medicine and Molecular Imaging (EANM/SNMMI) guidelines, based on both review of existing literature data and expert opinion, for the use of FDG in inflammation and infection reported an overall sensitivity of 95% and specificity of 98% for knee and hip periprosthetic infections with FDG-PET [12]. Moreover, the range for both sensitivity (28 to 91%) and specificity (34 to 97%) of the individual studies is quite large, which can be partly explained by the different study design and the lack of standardization in the interpretation criteria (visual interpretation using pattern recognition). Large prospective studies comparing the diagnostic performance of WBC scintigraphy and FDG-PET for PJI are required.

The American College of Radiology published their appropriateness criteria for imaging after total knee replacement [13]. After an extensive literature review by a panel of experts, they recommend that the use of three-phase bone scintigraphy and white blood cell scintigraphy (labelled with In-111 and with SPECT/CT if necessary for exact location) may be appropriate in the particular setting of pain after total knee arthroplasty when joint aspiration culture(s) are negative or inconclusive and the clinician still has strong suspicion of PJI.

Recently, in a well-designed study, Kwee et al. analyzed the added value of FDG PET/CT to conventional tests performed for the diagnosis of PJI, such as radiography, serum markers and synovial fluid-based tests [14]. They demonstrated that when erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were not elevated and/or serum tests were normal, FDG-PET/CT did not add any diagnostic value. Based on the available data, it is difficult to support the routine use of FDG-PET/CT for the workup of patients suspected of having PJI.

The American Academy of Orthopaedic Surgeons (AAOS) guidelines also state that the nuclear medicine imaging modalities are certainly an option for diagnosis of PJI in a selected group of patients suspected of PJI in whom diagnosis of PJI could not be reached or refuted, such as patient with failed attempts to retrieve synovial fluid. [15].

In summary, there is a role for nuclear imaging modalities in select group of patients with suspected PJI. However, they should not be used as a first diagnostic test. In patients with a low probability of PJI and not within the first years after surgery, three-phase

bone scintigraphy can be a good option. When negative, it excludes an infection. However, a positive result requires additional workup using other nuclear imaging modalities. White blood cell scintigraphy is then first choice because of its high diagnostic accuracy when correctly performed and interpreted. Antigranulocyte monoclonal antibody scintigraphy can be a second choice option for those centers that cannot perform labelling of the leukocytes. At this moment, routine use of FDG-PET/CT in patients with (suspected) PJI is not supported.

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QUESTION 4: What is the diagnostic accuracy of magnetic resonance imaging (MRI) for osteomyelitis in the presence and absence of implants?

RECOMMENDATION: MRI is useful for the diagnosis of osteomyelitis in the absence of metal implants, although there are other diagnostic tools that show greater specificity and sensitivity. The pooled sensitivity and specificity for MRI in diagnosing osteomyelitis without presence of implants are 84% and 60%, respectively. There are no identifiable studies on the diagnostic accuracy of MRI for osteomyelitis around metal implants. Several techniques for reducing metal artifacts exist.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 96%, Disagree: 1%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

Diagnostic Accuracy of MRI for Osteomyelitis in Absence of Implants

A variety of diagnostic imaging techniques are available for excluding or confirming chronic osteomyelitis, including plain radiography, computed tomography, bone scintigraphy, leukocyte scintigraphy, gallium scintigraphy, combined bone and leukocyte scintigraphy, combined bone and gallium scintigraphy, fluorodeoxyglucose positron emission tomography and MRI [1–6].

Each of these techniques have varying degrees of sensitivity, specificity and diagnostic accuracy. The Termaat's study [7] (Table 1) shows that the sensitivity and specificity of magnetic resonance imaging is sufficiently homogeneous (Q_{sens} = 4.62: four degrees of freedom, Q_{spec} = 0.02: two degrees of freedom) for chronic osteomyelitis in the peripheral skeleton and was not different from that of leukocyte scintigraphy or combined bone and gallium scintigraphy for the studies in this systematic review [7–28].

The literature demonstrates that MRI is useful for the diagnosis of osteomyelitis in the absence of metal implants, although there are other diagnostic tools that show greater specificity and sensitivity.

Diagnostic Accuracy of MRI for Osteomyelitis in Presence of Metallic Implants

There are no identifiable studies on the diagnostic accuracy of MRI for osteomyelitis around metal implants. There are five studies providing some information on this topic.

Jiang et al. [29] analyzed 16 patients who received tumor resection and joint replacement for bone cancer. They were retrospectively analyzed to identify MRI features that were useful for the

Table 1. Sensitivity and specificity of various imaging techniques [7]

Type of Study	Pooled Sensitivity (95% CI)	Pooled Specificity (95% CI)
Bone scintigraphy	82% (70% – 89%)	25% (16% – 36%)
Leukocyte scintigraphy	61% (43% – 76%)	77% (63% – 87%)
Combined bone and leukocyte scintigraphy	78% (72% – 83%)	84% (75% – 90%)
Fluorodeoxyglucose positron emission tomography	96 % (88% – 99%)	91% (81% – 95 %)
Magnetic Resonance	84% (69 – 92 %)	60% (38% – 78%)
Radiography	ND	ND
Computed tomography	ND	ND
Combined bone and gallium scintigraphy	ND	ND
Gallium scintigraphy	ND	ND

CI, confidence interval; ND, no data

diagnosis of periprosthetic infection and tumor recurrence using the optimized MRI parameters with and without view angle tilting (VAT) correction at 1.5 T in coronal fast-spin-echo T2-weighted MRI. Irregular soft tissue mass, soft tissue edema, bone destruction and fistula were significant features of periprosthetic infection, with sensitivities of 47.4 to 100% and specificities of 73.1 to 100.0%, which were confirmed based on surgical and pathological findings. Soft tissue masses were a significant feature of tumor recurrence, with 100% sensitivity, 96.0% specificity and 97.0% consistency.

Jungman et al. [30] found that significant reduction of artifacts was achieved by VAT ($p < 0.001$) and VAT and slice encoding for metal artifact correction (SEMAC) ($p = 0.003$) when compared with conventional pulse sequences. On clinical MRIs, artifact diameters were significantly reduced and diagnostic confidence improved ($p < 0.05$). In 2 cases tumor-recurrence was diagnosed, in 10 cases infection was diagnosed and in 13 cases other pathology was diagnosed.

Fritz et al. [31] mention that optimized conventional pulse sequences and metal artifact reduction techniques afford improved depiction of bone, implant-tissue interfaces and periprosthetic soft tissue for the diagnosis of arthroplasty-related complications. They present strategies for MR imaging factors and parameters for: (a) minimization of arthroplasty-related artifacts (imaging at 1.5 T, instead of 3 T, fast spin-echo (SE) sequence, instead of gradient-echo sequences, high receiver (readout) bandwidth, thin sections) and (b) optimization of image quality (use of intermediate echo time, which results in fluid-sensitive images, instead of T1-weighted or heavily T2-weighted imaging, large matrix in the frequency direction (e.g., 512), high number of excitations and inversion-recovery fat suppression, instead of frequency-selective fat suppression). They concluded that MRI is effective for the assessment of the periprosthetic soft tissues in patients who have had a total hip arthroplasty (THA).

Alprandi et al. [32] demonstrated the diagnostic value of MRI when measuring and characterizing periprosthetic fluid collections (classified as serous/purulent/hematic according to signal behavior). For all evaluations, inter-observer agreement was 100%. No significant differences were found between the measurements of the collections ($p > 0.258$). The authors agree that MRI is highly reproducible in detection, localization, quantification and characterization of fluid collections when the presence of implant infection is clinically suspected.

White et al. [33] investigated the use of standard MRI sequences with simple parameter modifications in 14 THAs for the detection and characterization of THA complications and conclude that by using simple modifications to standard MR imaging sequences, diagnostic-quality MR imaging of THA complications can be performed, particularly around the femoral prosthetic stem.

Magnetic Resonance Imaging Considerations

Attempts have been made to obtain a Metal Artifact Reduction Sequence (MARS) to reduce the size and intensity of magnetic susceptibility artifacts resulting from magnetic field distortion. Artifacts are encountered especially while imaging near metallic implants and result from local magnetic field inhomogeneities introduced by the metallic object into the otherwise homogeneous external magnetic field.

A variety of techniques are used for reducing metal artifacts in MRI. Some techniques proposed include single point imaging, prepolarized MRI, VAT, multiacquisition variable-resonance image combination (MAVRIC) and SEMAC. Changes to the scan protocol can address artifacts due to the presence of metal in the image plane (in-plane artifacts) and due to metal in an adjacent plane (through-plane artifacts) [34]. MAVRIC is a specialized sequence to minimize metallic artifact around metallic prostheses [35]. It relies on 3D fast spin echo (FSE) sequences, using multiple different overlapping volumes at different frequency offsets. Another technique used for addressing through-plane metal artifacts is SEMAC, where an additional slice-encoding gradient is added to a standard fast-spin echo sequence [36]. The combination of the MAVRIC and SEMAC technique is known as multiacquisition variable-resonance image combination selective (MAVRIC-SL) sequence[37].

Conclusions

The literature shows that MRI can be useful in the diagnosis of osteomyelitis in the absence of metal implants, although there are other diagnostic tools that show greater specificity and sensitivity. There is a paucity of data regarding the diagnostic value of MRI for osteomyelitis in presence of metallic implants. Several techniques for reducing the artifacts seen on MRI exist and others are in development, but there is no clinical data about the diagnostic accuracy of osteomyelitis for MRI in this setting.

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Treatment

3.1. TREATMENT: ANTIMICROBIALS

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QUESTION 1: What is the optimal choice and duration of antibiotic therapy in polymicrobial surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: The optimal choice and duration of antimicrobial therapy in polymicrobial PJIs remain unknown. Antimicrobial therapy for polymicrobial PJI should be targeted at the organisms that are present. There is limited literature on the antibiotic treatment as polymicrobial PJIs are very heterogenous. We recommend four to six weeks of intravenous or highly-available oral antimicrobial therapy, that is based on the in vitro susceptibilities of the individual microorganisms, patient allergies and intolerances.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 5%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Polymicrobial PJI, as identified by isolation of multiple organisms by culture, constitutes between 6% and 37% of reported PJI [1–4]. Patients with polymicrobial PJI have worse outcomes when compared to monomicrobial PJI and culture-negative PJI, regardless of the surgical treatment [5,6]. Studies have shown a lower success rates of polymicrobial PJIs (37 to 67%) compared to that of monomicrobial PJIs (69% to 87%) [5–9]. The treatment often requires broad-spectrum antibiotics or multiple antibiotics given that multiple organisms need to be targeted. Unfortunately, there is minimal literature regarding the optimal choice and duration of antibiotic therapy in patients with polymicrobial PJI. This is largely due to the fact that polymicrobial PJIs are very heterogenous and may represent many combinations of infecting organisms including fungi. However, there are many studies that have demonstrated that polymicrobial PJIs are associated with certain bacteria. Marculescu et al. found that methicillin-resistant *Staphylococcus aureus* (26.4% versus 7.1%) and anaerobes (11.7% versus 2.8%) were more common in polymicrobial PJIs. In addition, Tan et al. reported that the isolation of gram-negative organisms ($p < 0.01$), enterococci ($p < 0.01$), *Escherichia coli* ($p < 0.01$), and atypical organisms ($p < 0.01$) was associated with polymicrobial periprosthetic joint infection. Furthermore, many of these organisms are associated with high failure rates and the optimal antimicrobial for these organisms are still being defined [10,11].

While there are no randomized studies to compare the duration of treatment for polymicrobial PJIs compared to monomicrobial PJIs, patients treated for polymicrobial PJIs received four to six weeks of antimicrobial therapy [6–8], with the choice of an initial two weeks of parenteral antimicrobial therapy followed by four weeks of oral and highly-bioavailable antibiotic therapy [7,8]. Current Infectious Disease Society of America (IDSA) guidelines, while not specifically addressing polymicrobial PJIs, suggest four to six weeks of pathogen specific intravenous or highly-bioavailable oral antimicrobial therapy, which does not differ from the treatment of monomicrobial PJIs [12].

A study done by Moran et al. on 112 patients showed that polymicrobial organisms were present in 46.7% in the early postoperative period (within 3 months after prosthesis implantation) [3]. While in this study gram-negative organisms were seen only in 8% of the polymicrobial isolates, among these isolates were organisms classically associated with chromosomal Amp C-inducible beta-lactamases (*E cloacae, Serratia spp, Morganella morganii),* and resistant *Acinetobacter spp.* These findings, along with a high rate of beta-lactam resistance among coagulase-negative staphylococci (CoNS) have led the authors to recommend a broad-spectrum empirical antimicrobial coverage with a glycopeptide and a carbapenem [3]. In contrast, a study by Sousa et al. found no increased prevalence of polymicrobial infection in the early postoperative period, but they too recommend a carbapenem and vancomycin as empirical antimicrobial therapy for chronic and hematogenous infections when polymicrobial infection was present [13].

When selecting empirical antimicrobial therapy for polymicrobial PJIs, it is therefore important to be aware of the local and institutional gram-negative and gram-positive resistance pattern. Broad-spectrum antimicrobials should be stopped as soon as susceptibility results are available and effective antimicrobials with the narrowest spectrum of activity should be selected for completing the therapy.

Given that outcomes are poor with polymicrobial PJIs, chronic suppression may be warranted as multiple studies have demonstrated increased survivorship with the addition of oral antibiotics [14,15]. Frank et al. demonstrated that patients treated with oral antibiotics failed secondary to infection less frequently than those not treated with antibiotics (5% versus 19%, $p = 0.016$) in a prospective randomized controlled trial [14].

Search Methodology: A PubMed Search for the MeSH Terms ((“Infection”[MeSH]) AND (“Prostheses and Implants”[MeSH] OR “Prosthesis Implantation”[MeSH] OR “Prosthesis-Related Infections”[MeSH] OR “Prosthesis Failure”[MeSH])) AND “Coinfection”[MeSH] as well as for the terms polymicrobial[All Fields] AND (“joints”[MeSH Terms] OR “joints”[All Fields] OR “joint”[All Fields]) AND (“infection”[MeSH Terms] OR “infection”[All Fields]) on February 12, 2018 revealed a total of n = 161 results. All publications were screened and evaluated for relevance regarding the research question and duplicates.

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QUESTION 2: What systemic antibiotic therapies should be used in patients with surgical site infection/periprosthetic joint infection (SSI/PJI) caused by resistant organisms?

RECOMMENDATION: The choice of antibiotic therapy in patients with SSI/PJI caused by resistant organisms is not fully answered by literature. There are a number of antibiotic choices available for patients with SSI/PJI caused by resistant organisms. The antibiotic selection process should consider patient comorbidities, mode of administration, risk of Clostridium difficile, need for monitoring, allergy profile of the patient, intolerance, regional resistance patterns, cost and availability. Ideally, apart from having activity against the resistant organisms, antibiotic choice should have good bone and soft tissue penetration and activity against biofilm. Consultation with infectious diseases specialists and clinical microbiologists is warranted in these cases.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 2%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

Success rates in the treatment of PJI produced by resistant bacteria are lower than those from sensitive organisms, resulting in an increase in morbidity and cost. Successful treatment requires a multidisciplinary approach, including orthopaedic surgeons, infectious diseases specialists and microbiologists with an interest and experience in treating these complex infections.

Relative resistance is conferred by biofilms even when treated with susceptible antimicrobials, particularly in debridement and implant retention (DAIR). Antimicrobial decision-making needs to consider not only the minimum inhibitory concentration (MIC) but also the minimum biofilm-inhibitory concentration (MBIC) and minimum biofilm bactericidal concentration (MBBC), if performed.

Staphylococcus, streptococci, enterococci, enterobacteriae such as *Escherichia coli* or *Klebsiella pneumoniae*, *Pseudomonas*, and Candida are common microorganisms that form biofilms and are implicated in PJI [1]. The biofilm results in physiological, physical and adaptive resistance mechanisms to commonly-used antibiotics in PJI including aminoglycosides, β-lactams, quinolones and glycopeptides [2].

The transcriptional inhibitor rifampin has demonstrated consistent antibiofilm activity in gram-positives and is recommended by the Infectious Diseases Society of America (IDSA). Fluoroquinolones are the first choice as antibiofilm agent in gram-negative infections. Colistin and fosfomycin could be alternatives [1].

Gram-positive PJI/SSI

The main gram-positive PJI are *Staphylococcus aureus* and *Staphylococcus epidermidis*. Methicillin resistance is more common in *Staphylococcus epidermidis* (MRSE) compared to *Staphylococcus aureus* (MRSA). The majority of clinical studies include both MRSA and MRSE sharing treatment options. *Enterococcus spp*. is a rare cause of gram-positive PJI including vancomycin resistant *enterococcus* (VRE).

The initial therapy for MRSA or MRSE PJI infections after debridement should be directed against planktonic cells and is currently based in glycopeptides [3]. However, at high inocula vancomycin's efficacy is often suboptimal and in monotherapy poor clinical data have been published [4]. Interestingly the combination of daptomycin plus oxacillin has shown synergy in in vitro MRSA models, also against biofilm-embedded bacteria [5–7]. Although clinical experience is lacking, this combination could be used in the first days of MRSA PJI infection.

After the initial acute period (one to two weeks), targeted antibiofilm therapy is warranted. As stated previously, rifampin has

excellent activity against staphylococci in biofilm [8]. There is some indication that rifampin in combination with other anti-staphylococcal agents may improve the outcome of treatment. This was highlighted by one of the few clinical randomized controlled trials on antibiotic use in PJI. In patients with staphylococcal infection surgically managed by DAIR, the addition of rifampin to flucloxacillin or vancomycin for two weeks and three to six months of ciprofloxacin improved cure rate from 58% to 100% compared to antibiotics with a rifampin placebo [9]. The latter study has been criticized for consisting of a very small number of patients and its findings have not been embraced by the entire orthopaedic community. It is important to note that rifampin monotherapy is associated with a high likelihood of resistance and is not recommended by IDSA guidelines. Many methicillin-resistant staphylococcal PJI are also resistant to fluoroquinolones. However, if susceptible, it combines well with rifampin with good outcomes [9–12]. This combination has a good bioavailability, activity and safety, as has been shown in several clinical studies and it is considered the first choice if the *Staphylococcus* is susceptible to both agents [9,11–14]

There are numerous combinations with rifampin suggested in the literature for resistant staphylococci and alternatives if rifampin cannot be used. The majority of clinical studies are non-comparative retrospective reviews. The animal studies and in vitro studies provide comparative results, but there is little consensus and different methodologies used limit meta-analysis to make conclusions. A number of studies compare the following agents in combination with rifampin: vancomycin, daptomycin, linezolid, cephalosporins, carbapenems, fosfomycin, tigecycline, minocycline, fusidic acid, co-trimoxazole. Vancomycin is often the first line in MRSA/MRSE PJI [15]. A number of studies have concluded that year-on-year MRSA strains have a higher vancomycin MIC [16,17]. Some studies have demonstrated improved efficacy with vancomycin and rifampin in vitro [18], but this combination also results in rifampin resistance [19]. In comparison to levofloxacin, daptomycin has favorable results when combined with rifampin in vitro. Monotherapy use produced rifampin and daptomycin resistance and should be avoided [20,21]. Compared with linezolid and vancomycin, animal studies similarly favored daptomycin and rifampin [21–23]. A similar animal study comparing linezolid, vancomycin and daptomycin as a monotherapy and in combination concluded superiority of the daptomycin rifampin combination [24]. Clinically, non-comparative series using daptomycin achieved good outcomes if the implant is removed with 91% (10/11) [25] and 100% (22/22) [26] success with two-stage revision, respectively. Poorer results occurred after debridement and implant retention using daptomycin and rifampin, with success rates ranging from 50 to 80% (4/5, [25], (6/12, [27]) (9/18, [28]).

The fifth-generation cephalosporin, ceftaroline, is an option with similar activity to vancomycin and improved side effect profile. It is more effective in combination with rifampin in MRSA animal models [29]. An in vitro biofilm study, in contrast, concluded that the addition of rifampin to ceftaroline was not beneficial and antagonistic with some MRSA strains. They found that ceftaroline and daptomycin combination was the most effective but accepted that in vivo studies were required before its clinical applicability is known [30].

Tigecycline has been investigated as an alternative in MRSA PJI. Animal models comparing it to vancomycin as monotherapy or combined with rifampin concluded it was as effective as vancomycin with rifampin, but tigecycline alone was least effective [31]. Tigecycline combined with other antimicrobials produces an indifferent response, but has been shown to be effective against multi-resistant gram-positive and gram-negative organisms and could be considered as part of a combination regimen when first- and second-line options are contraindicated [32,33].

Thompson et al. compared 10 antibiotic groups in a MRSA animal model. The study did not confirm superiority, but that linezolid, vancomycin, daptomycin, ceftaroline in combination with rifampin were successful at eradicating bacteria. No antibiotic monotherapy cleared the bacteria [34].

In comparison to the oral antimicrobials fusidic acid, linezolid, rifampin and minocycline, linezolid was the only monotherapy effective against biofilm-embedded MRSA [35]. In an animal methicillin-susceptible *S. aureus* (MSSA) model, linezolid with rifampin prevented rifampin resistance and demonstrated superior activity compared to linezolid alone or cloxacillin with or without rifampin [36].

The retrospective clinical results of linezolid with rifampin following DAIR achieved successful remission in 69% (34/49). Linezolid was used as second line where previous treatment failed or therapy intolerance [37].

Another retrospective review of 39 gram-positive cocci PJI, remission of infection was achieved in 72% using linezolid following DAIR. Some patients also received rifampin which in this series was associated with a higher failure rate of 36% vs.18% which the authors commented that the rifampin group had a higher proportion of MRSA, diabetes and longer symptom duration before DAIR [38].

Combinations of rifampin plus linezolid have shown an increase in the antibacterial effect of linezolid in biofilm and a synergic activity against MRSA isolates [19,35,36]. Clinical series have demonstrated acceptable clinical outcome, although the studies are heterogeneous [37–39]. It is not well established the possible effect of rifampin in metabolism of linezolid. In vivo studies such as that by Gandelman et al. [40] showed that the combination is safe and well-tolerated, with only a small effect on the clearance of linezolid.

Results of co-trimoxazole and fusidic acid highlight that they still have a role in resistant staphylococcal PJI. Lower cost and oral administration are advantageous if the microorganisms are susceptible. A study of 56 bone and joint infections, including 36 with infected implants, received either linezolid or co-trimoxazole in combination with rifampin. There was no significant difference in cure rates with 89.3% success with linezolid and 78.6% with co-trimoxazole [41]. Co-trimoxazole has historically been an oral agent active against resistant staphylococcal infections, achieving success in 67% in a prospective study of 39 PJI. Treatment was between six and nine months. Device removal improved outcomes, but 60% were successful with implant retention [42].

A large retrospective review of 345 *Staphylococcus aureus* PJI managed with DAIR concluded that there was no difference in success between β-lactams or quinolones for MSSA or glycopeptides, co-trimoxazole, linezolid or clindamycin for MRSA in a series where 88% were used in combination with rifampin. Overall success was 55%, of which 80% had received rifampin for over 4 weeks [11].

Options in Rifampin Resistance

Rifampin resistance in association with resistant organisms is associated with inadequate surgical debridement or inadequate combination antibiotic treatment [43]. The IDSA recommends a four-to-six-week intravenous course of antibiofilm-guided therapy in rifampin resistance [44].

Fosfomycin has been investigated as an alternative to rifampin in gram-positive resistant PJI. Vancomycin with fosfomycin or rifampin were superior to tigecycline for planktonic bacteria and vancomycin combinations with fosfomycin or minocycline was superior for antibiofilm activity [18]. Fosfomycin with daptomycin was as effective as daptomycin-rifampin. Fosfomycin-imipenem was ineffective and resulted in resistance [23]. An in vitro biofilm comparison model found higher rifampin resistance with vancomycin, teicoplanin, daptomycin and tigecycline [19] A similar model

used the same antibiotics, except daptomycin, but combined them with fosfomycin. They concluded that fosfomycin enhanced activities of linezolid, minocycline, vancomycin and teicoplanin and was superior to rifampin combinations [45].

Interestingly an animal model study suggested that rifampin resistance can be transient and that rifampin-based combination therapy can be effective even if rifampin-resistant bacteria was previously selected by rifampin exposure [46].

Some studies have even demonstrated that using resistant antibiotics in combination with a non-resistant antibiotic may be effective. Combining cloxacillin with daptomycin was active in an MRSA animal model [5] and was as effective as cloxacillin with rifampin in an MSSA model in rifampin resistance [6]. In vitro and in vivo lab studies have demonstrated synergy between daptomycin and β-lactams or carbapenems including nafcillin, cefotaxime, amoxicillin-clavulanic and imipenem. Combination therapy prevented daptomycin resistance [7]. An in vitro MRSA biofilm study concluded that neither daptomycin nor linezolid were active against biofilm embedded bacteria however in combination they were successful [47]. In other studies, linezolid monotherapy exhibited excellent inhibitory effects against biofilm-embedded MRSA [19,45]. There is considerable literature on the use of linezolid in monotherapy, showing high success rates [38,48–50]. Its excellent bone and tissue penetration is one of the main reasons for this. So, it could be an alternative in rifampin resistant staphylococcal infections.

Drug Interaction and Concentration Levels

Although the majority of studies demonstrate a benefit from combination therapy, drug interactions and pharmacokinetics must be considered. A randomized control trial comparing fusidic acid with rifampin versus vancomycin was stopped. The authors identified that the fusidic acid concentrations were lower than expected and at low levels rifampin resistance occurred [51]. In contrast, a study of 62 patients taking rifampin and fusidic acid demonstrated pharmacokinetics resulting in high drug exposure [52]. Decreased trough clindamycin concentrations were associated with concomitant rifampin use in an observational study of 61 patients infected with gram-positive organisms [53]. A crossover study into the pharmacokinetics of linezolid in combination with rifampin in 16 healthy adults demonstrated an interaction resulting in increased linezolid metabolism resulting in a lower concentration for the dosing interval [40].

Enterococcus

Enterococcal PJI is rare (3 to 10%) and associated with high failure rates [54]. Unlike rifampin in staphylococcal PJI there is no antibiofilm agents active against *Enterococcus*. Strains can be penicillin-susceptible, penicillin-resistant or vancomycin-resistant. IDSA guidelines recommend combination therapy with aminoglycosides. Typical combinations of gentamicin with ampicillin for penicillin susceptible, vancomycin for penicillin resistant and linezolid or daptomycin for vancomycin resistant are recommended. In vitro and animal studies of *E. faecalis* had cure rates of 17% with vancomycin, 25% with daptomycin, 33% with vancomycin and gentamycin and 55% with daptomycin and gentamycin [55]. Fosfomycin with gentamicin was shown to be superior to vancomycin and daptomycin with eradication of *E. faecalis* in 42%. Combinations of cephalosporins, ampicillin, aminoglycosides, daptomycin and linezolid are options for VRE PJI but there is no consensus across the literature and clinical series are too small and heterogenous to make firm conclusions on antibiotic therapy. Due to the low success treating these resistant organisms that lack antibiofilm therapy DAIR is unlikely to work and aggressive surgical management is required.

Gram-negative PJI/SSI

Ten to 30% of PJIs are caused by gram-negative bacteria. These include *Escherichia coli, Pseudomonas aeruginosa*, *Klebsiella* species, *Proteus* species, *Pasteurella* species and *Serratia spp*. [56,57]. Appropriate antibiotics include cephalosporins, carbapenems and fluoroquinolones often in combination, directed by antibiofilm including fluoroquinolones in the combination when susceptible. Colistin and fosfomycin have good biofilm activity and can be used in combination, particularly against fluoroquinolone resistant organisms. Extended spectrum β-lactamase (ESBL) producing enterobacteriaceae, *Klebsiella pneumoniae* carbapenemase producing (KPC) enterobacteriaceae and Pseudomonas strains are resistant to a variety of antibiotics and are difficult to eradicate.

Like the biofilm in gram-positive organisms, many gram-negative organisms demonstrate resistance to phagocytosis when adherent to the surface of implants even when treated with susceptible antibiotics. Clinical outcomes of gram-negative PJI in the literature vary between high rates of success, even following DAIR or small series of very difficult to treat infections where despite combination antibiotics and aggressive surgical management with staged revision they have low rates of success. Fluoroquinolone sensitivity or resistance explains the dichotomy. Fluoroquinolones have good activity against *E. coli* due to efficacy against non-growing and adherent bacteria [58]. A retrospective series of 17 gram-negative infections managed with debridement and implant retention achieved successful remission in 15. Antibiotic use included intravenous cephalosporins or carbapenams initially followed by medium term oral ciprofloxacin. The authors concluded that the ciprofloxacin provided good antibiofilm activity [59]. A retrospective review of 24 gram-negative bone infections successfully eradicated infection in 79% using a combination of cefepime and fluorquinolone. Approximately half were treated with device retention and half with removal but there was no difference in success [60]. Ceftazidime and ciprofloxacin combination therapy was effective with implant retention in 24 pseudomonas infected implants [61]. A large retrospective series of 242 gram-negative PJI infections also demonstrated that including fluorquinolones in the combination therapy had higher successful rates [62].

Carbapenam-resistant *Klebsiella pneumoniae* has advanced mechanisms to rapidly generate resistance on therapy, including colistin and aminoglycosides. A failure to respond to treatment warrants not only a change of antibiotics but repeated debridement and new samples for sensitivity testing [63]. An animal model of KPC-producing *Enterobacteriaceae* demonstrated that synergistic combinations of tigecycline with rifampin or gentamicin were effective whereas there was antagonism using a combination of tigecycline with meropenem or colistin [64].

An in vitro and animal study of fluoroquinolone resistant *Escherichia coli* comparing fosfomycin, colistin, tigecycline, gentamycin, alone and in combination concluded the highest cure rate was with fosfomycin and colistin. Fosfomycin was the only monotherapy able to eradicate ESBL-producing *E. coli* biofilms [65].

IDSA guidelines recommend combination therapy for *Pseudomonas* PJI due to the limited antibiotic options [44]. In vitro studies combining fluoroquinolones with β-lactams or aminoglycosides reduces the risk of resistance to *Pseudomonas* and *Acinetobacter spp*. [66,67]. Multidrug resistant *Pseudomonas* was more effectively treated by combination therapy of colistin with β-lactams (cure rate 11/15) compared to monotherapy (cure rate 6/19) [68].

Interestingly, combining drugs even if one of them is resistant can be associated with antimicrobial activity. An in vitro study of biofilm and planktonic multidrug resistant *Pseudomonas aeruginosa* concluded that colistin in combination with doripenem was effective against both carbapenem susceptible and resistant strains and

reduced colistin resistance. The role of the carbapenem is to prevent colistin resistance, not treat the resistant organism [69].

Some newly-approved antibiotics for resistant gram-negative infections utilize the synergy of antibiotic combinations. Ceftazidime/avibactam and ceftolozane/tazobactam combine second generation β-lactamase inhibitors with cephalosporins. In vitro activity is demonstrated against multiple drug-resistant gram-negative organisms including *Pseudomonas* and KPC producing Enterobacteriaceae. Clinically they are licensed for ventilator associated pneumonia, compliated intra-abdominal infections and complicated urinary tract infections [70] Currently, there are no studies specifically using these novel drugs in PJI.

Fungal PJI

Less than 1% of PJI are due to fungal infections. They are often associated with multiple revisions for infection, immunosuppression and prolonged antibiotic therapy [71,72]. Candida is the most common species and is known to produce a complex biofilm conferring rapid resistance. IDSA guidelines recommend fluconazole initially but ultimately based on antifungal susceptibility testing. Antibiofilm activity can require high antifungal doses associated with systemic toxicity, therefore staged arthroplasty and use of antifungal bone cement is routinely advocated. Amphotericin B [73] or voriconazole [74] is heat-stable and achieve high local concentrations.

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QUESTION 3: Should periprothetic joint infection (PJI) caused by *C. acnes* be treated the same as other bacterial causes of PJI?

RECOMMENDATION: Yes. PJIs caused by *C. acnes* should be treated in the same fashion as other causes of PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

C. acnes is a non-spore-forming, gram-positive, facultative bacillus classified as an anaerobe with aerotolerant properties [1–3]. *C. acnes* has previously been categorized as a laboratory handling contaminant and is considered nonpathogenic, largely due to the presumed commensal nature of the bacterium, as well as identification on normal skin flora and maintenance of the microbiome [2,4]. Despite previous thinking, *C. acnes* is becoming increasingly recognized as an opportunistic and pathogenic organism in orthopaedic surgery. *C. acnes* often presents in a subacute or delayed manner due to an indolent clinical presentation and unreliable utility of classically used markers of infection, however this organism may represent 6 to 10% of orthopaedic infections [2,5–9]. It is speculated that *C. acnes* colonizes the surgical site at time of prosthesis implantation and grows unrecognized by the body through biofilm formation [10–12]. In the shoulder, the clinical and traditional inflammatory laboratory indicators of infection with *C. acnes* are often within normal limits, however its presentation during hip and knee arthroplasty infection may be more overt with classical signs and symptoms of infection [8,13]. Accurate identification of *C. acnes* requires long hold cultures up to 14 days, which is likely why this organism has previously been under-appreciated as the cause of orthopaedic infections [2,3].

In the orthopaedic literature, *C. acnes* has been identified as both a possible commensal organism observed at the time of surgery and as a definite pathological bacterium implicated in orthopaedic implant related infections. One prospective study evaluating intraoperative cultures showed *C. acnes* to be present in 8.5% of skin cultures, 7.6% of superficial cultures and 13.6% of deep cultures at the time of primary shoulder surgery [14]. The prevalence of *C. acnes* in patients undergoing revision shoulder arthroplasty has been shown to exceed that of other common offending organisms, with a recent study showing 38% of patients having a positive *C. acnes* culture [15]. A recent study utilizing next-generation sequencing in patients presumed to be undergoing aseptic revision hip and knee arthroplasty isolated microbial DNA in 27% of patients with *C. acnes* being the most prevalent organism [16].

Previous work has attempted to distinguish between these commensal and pathogenic strains through phylotype associations and phenotypic markers of the bacteria such as hemolysis [17,18]. A distinct pathogenic phenotype has yet to be clearly associated with true clinical infections, however phylotypes IB and II have most commonly been implicated in orthopaedic infection [17]. These phylotypes have varying adaptive virulence properties that may influence pathogenic potential, including the ability to degrade and invade host cells, produce an enhanced host inflammatory response, form biofilms and demonstrate antibiotic resistance [19–21]. Beta-hemolytic activity has been noted in certain strains of *C. acnes* and may be directly correlated with the bacteria's pathogenicity [18]. The hemolytic Christie-Atkins-Munch-Peterson (CAMP) factor is found in the *C. acnes* genome and functions as a toxin to host cells, which may be responsible for this observed beta-hemolytic activity [20,22]. A *C. acnes* hemolytic phenotype observed on brucella blood agar media has been shown to be a marker of definite infection with 100% specificity and 80% sensitivity along with an increased pattern of antibiotic resistance [18,23]. Suggestions of enhanced virulence of *C. acnes* have been implicated when it serves as a co-infectant with other bacterial species, which may be why at times it is found in polymicrobial cultures and erroneously characterized as a contaminant in some clinical situations [24,25].

Pathogenic *C. acnes* strains are well-known to form a robust biofilm on implant surfaces resistant to antibiotic penetration, similar to more commonly recognized bacterial pathogens [20,26,27]. Implant biofilm is difficult to treat without implant removal and reported treatment success of a *C. acnes* PJI has been variable with treatments involving implant or polyethylene retention having the poorest results [13,28,29].

Currently, there are no prospective studies evaluating varying treatment strategies of *C. acnes* orthopaedic infection, with most studies being retrospective in nature. Retrospective studies evaluating various treatments for shoulder, hip, knee and spine *C. acnes* infection have reported variable success [13,28–30]. Studies evaluating total shoulder arthroplasty (TSA) and upper extremity infection have shown good outcomes with treatments involving one or two-stage revision procedures with success rates ranging from 74 to 95% [5,13,31,32]. One retrospective analysis found nonsurgical treatment with four to six weeks of intravenous antibiotics led to 67% of patients not requiring subsequent surgical management as compared to 71% of patients not requiring further surgery after initial surgical management [33]. Two studies evaluating all orthopaedic infections caused by *C. acnes* reported a 100% failure rate when partial or no implant removal was performed with success rates ranging from 62 to 75% when one and two-stage exchanges were performed [28,29]. A similar retrospective study evaluating hip, knee and shoulder arthroplasty PJI with *C. acnes* showed a 95% success rate in TSA PJI treated with a two-stage procedure while those treated with an irrigation and debridement (I&D) with component retention had a 37% success rate [13]. Hip and knee success rates in the same study were lower when a two-stage procedure was utilized at 67% and 64% respectively. However, other studies have reported success rates as high as 94% to 100% with a two-stage exchange for hip and knee PJI with *C. acnes* [13,30]. One retrospective study specifically evaluated *C. acnes* total knee arthroplasty (TKA) PJI treated primarily with two-stage exchange and I&D with liner exchange as compared to methicillin-sensitive staphylococcal TKA PJI. This study showed similar success rates between treatment groups and suggested a PJI treatment strategy similar to methicillin-susceptible *S. aureus* (MSSA) TKA PJI be performed for *C. acnes* TKA PJI [8].

C. acnes has also been noted as a common pathogen in spine surgery with one large study showing *C. acnes* representing 9.7% of positive cultures [9]. Similar treatment strategies with partial and complete hardware exchange have been evaluated in the literature

with patients having partial implant removal resulting in inferior infection eradication rates as compared to those patients who had complete exchange of spinal components [9,34].

C. acnes is usually susceptible to beta lactams, quinolones, clindamycin and rifampin, but resistance is emerging and antibiotic susceptibility testing should be considered for PJI [23]. There is no general consensus on how to treat these infections. Many recommend three to six months of antibiotic treatment, including two to six weeks of intravenous (IV) treatment with a beta lactam, but no randomized controlled trials have been performed and some studies favor shorter treatment durations [20]. Given the lack of randomized controlled trials, following the Infectious Disease Society of America (IDSA) guidelines of four to six weeks' duration is recommended [35].

The role of rifampin is also unclear. An in vitro study showed activity against *C. acnes* biofilms [36]. One low-quality retrospective cohort study in patients with a primary or revision joint arthroplasty of the shoulder, hip or knee evaluated the role of rifampin in combination therapy and showed no difference in treatment success [37]. There are currently no randomized controlled human studies on the efficacy of rifampin in combination anti-microbial treatment for *C. acnes* PJI. Given the limited data, the addition of rifampin to the treatment regimen is not recommended at this time.

Although no prospective studies are currently available regarding the optimal treatment strategy for *C. acnes*, careful review and synthesis of the available literature suggest *C. acnes* be considered a true pathogen when the appropriate constellation of findings are present. When *C. acnes* PJI is identified, treatment algorithms should model after those of other invasive offending organisms. Caution should be taken when treating *C. acnes* PJI without explantation of exchangeable components or efforts to eliminate biofilm on retained implants due to the low success rates of simple irrigation and debridement with component retention.

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QUESTION 4: What is the most effective antibiotic in the treatment of *C. acnes* periprosthetic joint infection (PJI)?

RECOMMENDATION: Unknown. High rates of susceptibility to narrow spectrum beta-lactams make these a good initial intravenous (IV) option, though the optimum oral switch is not known. The role of rifampin is controversial. Prospective clinical studies are required to determine the optimal antimicrobial therapy for *C. acnes* PJI.

LEVEL OF EVIDENCE: No evidence

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

C. acnes is an anaerobic gram-positive bacillus and a common skin commensal found deep in sebaceous glands and hair follicles. As well as being commonly implicated in acne vulgaris, it is a well-recognized pathogen of device related infection including prosthetic joints [1–4].

The ability of *C. acnes* to form biofilm is a major virulence factor in the development of these infections, including PJI, and is an important consideration for optimizing treatment strategies. Management should follow well recognized guidelines of a combination of surgery and targeted antibiotic therapy [5–7], though this has been challenged by at least one retrospective analysis [8]. Pragmatically, however, without doing prospective studies and controlling for the surgery performed, the duration of therapy and individual host factors, comparisons of different antibiotic regimens in the real world are very difficult.

This problem is compounded by the difficult issue of determining the significance of cultured *C. acnes* from orthopaedic specimens, as it is a common and well-recognized contaminant. It has been shown to be present in fluid washed across the skin incision [9], has been found on surgeons' gloves after handling the subdermal layer [10] and is not reliably removed from the skin by surgical skin antisepsis [11]. The multiple sampling method of Atkins et al. [12] is commonly used to aid interpretation of the significance of *C. acnes* isolates, with one specimen positive out of three to five usually being deemed a contaminant [12]. The recommended duration of incubation of enrichment broths has been extended in recent years to 10 to 14 days to improve the pick-up rate of relatively slow-growing *C. acnes* in these samples. By increasing the isolation of significant isolates, however, the rate of contaminants also increases and requires careful interpretation [13]. It has been suggested that those isolated from true infections flag earlier than those that represent contamination. Sonication is recommended by some to improve pick-up rates of *C. acnes* associated with biofilm [14]. Some authors have gone further, by creating scoring systems to aid identification of true *C. acnes* infections [3,4].

For these reasons, accurate identification of *C. acnes* PJIs retrospectively is fraught with difficulties and thus interpretation of the outcome data comparing treatment strategies is very limited. The clinical details are imperative to aid interpretation. As well as varying in the clinical information available, retrospective studies also often span many years or decades, and straddle changes to sampling methods, culture methods and recommended duration of enrichment cultures. These differences further limit the ability to draw detailed comparisons between different interventions.

In vitro susceptibilities of *C. acnes* are reported widely. Surveillance studies show it remains susceptible to many antibiotics commonly used in treatment of bone and joint infection, but with increased and variable resistance to macrolides, clindamycin, tetracyclines and trimethoprim-sulfamethoxazole. A European surveillance study showed wide variations in rates of resistance across Europe, confirming the need to undertake susceptibility testing for individual isolates [15] and this has been replicated in other smaller series [15,16]. Looking at isolates from clinical specimens taken at shoulder surgery, Crane et al. showed that rates of resistance to beta-lactams (e.g., penicillin, amoxicillin, cefalozin and ceftriaxone) remained very low [17,18]. However, they found slightly higher minimum inhibitory concentrations (MICs) to vancomycin and taking that information with the minimum biofilm eradication concentration (MBEC) from other studies [19,20], vancomycin may be less favorable than alternatives in the context of biofilm. This study also looked at quinolones (ciprofloxacin and moxifloxacin) but not levofloxacin and showed high rates of susceptibility.

It is well-recognized that the susceptibility of microorganisms is dramatically reduced in biofilms. For infections with staphylococci, there is good evidence for the use of rifampin in combination therapy for its biofilm effect. The use of dual therapy with rifampin for *C. acnes* infections is theoretically attractive, though there is controversy in the literature. Bayston et al. found that linezolid plus rifampin led to relapse-free eradication after 14 days compared to linezolid alone [5]. Interestingly, in this study, penicillin alone was as effective as linezolid and rifamcin, but the effect of rifampin and penicillin was not examined. Tafin et al. in 2012 used an experimental foreign-body infection model to determine MIC and MBEC with and without rifampin for *C. acnes* from cage fluid and from explanted cages [19]. There was good activity of all antimicrobials tested for the planktonic forms, but rifampin was needed for activity in the biofilm. They used an in vivo animal model to evaluate susceptibility to levofloxacin, vancomycin, daptomycin and rifampin. The highest cure rate was found with daptomycin and rifampin (63%) followed by 46% for vancomycin and rifampin combination. Emergence of rifampin resistance associated with the presence of the rpoB gene has, however, been shown to occur in vitro [21].

Combination therapy for *C. acnes* has been further examined in vitro by Khassebaf et al. [15] who took *C. acnes* isolated from orthopaedic implant infections and carried out susceptibility testing in addition to looking for synergistic, additive and antagonistic effects of combinations. None of the antimicrobials examined were synergistic with each other and antagonistic effects were rare. Interestingly, the combination of rifampin and benzyl penicillin showed an additive effect on almost 50% of isolates tested. However, a retrospective cohort study by Jacobs et al. [22] showed no significant difference in success after two years between groups treated with combination antimicrobial treatment including rifampin (88%) or not including rifampin (82%). The most used antimicrobial in combination with rifampin was clindamycin.

The performance of these antimicrobials in clinical studies is not easy to assess and there are very few published good quality studies with no prospective studies identified and limited utility of retrospective studies. Over a decade ago, Zeller et al. conducted a retrospective cohort study of 50 patients with *C. acnes* PJI [23]. Treatment involved surgery with antibiotics for the majority of patients. Intravenous therapy with cefazolin and rifampin was administered to 24/50 patients and clindamycin with rifampin to 11 cases for a duration of 5 +/- 2 weeks followed by oral step down for a further 16 +/- 8 weeks. Oral regimens were similar to the IV regimes: cephalexin and rifampin or clindamycin and rifampin [23,24].

Reinmuller's retrospective review of a tertiary infection center database included 24 cases of *C. acnes* PJI over 14 years [25]. A strength in this study, despite it being retrospective, was the use of contemporaneous clinical diagnosis of infection alongside the microbiological diagnosis. All patients underwent surgery and were treated with antibiotics but the specifics of antimicrobial treatment are not given, other than stating that they followed recommendations by Zimmerli [7] and were guided by the specific antibiogram. Lutz reports 52 cases over 7 years but differences in outcome between antimicrobial regimes were not given [3].

In summary, there are no randomized control trials (RCTs) or formally conducted comparative studies of specific antibiotic combinations for the treatment of *C. acnes* PJI. Publications are confounded by difficulties and variations in definitions of infection, likely mixing true infections with contaminated cases. Surveillance studies suggest *C. acnes* remains highly susceptible to beta-lactams which are attractive from an antimicrobial stewardship point of view and are commonly used and recommended in Infectious Disease Society of America (IDSA) guidelines [4–7,22,26,27]. Increasing rates of resistance for clindamycin and doxycycline are seen and antimicrobial therapy must therefore be based on the susceptibility testing of infecting pathogens determined using accredited methods. Additive or synergistic testing might be helpful, but the utility of this needs corroboration in clinical studies. Determining an appropriate targeted regimen at this stage can only be based on in vitro susceptibilities, on knowledge of oral bioavailability and bone penetration and on an individual risk/benefit assessment for the use of rifampin and other agents. Both the best oral antimicrobial and the role of rifampin as part of combination therapy remain unclear and well conducted prospective RCT studies are needed to help answer these questions.

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QUESTION 5: What antibiotic therapy and duration should be used in surgical site infection/periprosthetic joint infection (SSI/PJI) caused by *Mycobacterium tuberculosis* (TB)?

RECOMMENDATION: TB PJI must be treated in collaboration with an infectious diseases specialist noting that the duration of treatment (minimum six months and up to two years) and the type of antimicrobials (usually a combination of four drugs) is determined based on the resistance profile of the pathogen.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 1%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

The review of the available literature on PJI caused by TB is mainly based on retrospective cohort studies and case reports. Our exhaustive search of the literature revealed a total of 44 publications reporting on 62 patients with PJI caused by TB, over a period of 40 years [1–44].

Eight of the studies did not report on the type of antibiotic treatment utilized [1–8]. In other studies, reporting on the antimicrobial treatment, 3 patients were treated by a two-drug combination regimen [9] and 23 patients received a three- or four-drug therapy [10–32]. Four patients were treated with more than four drugs [33–36]. Regarding the length of treatment [37], it was 6 to 9 months in 10 patients [38], 9 to 18 months in 21 patients and more than 18 months in 19 patients [39]. Based on the literature, only three patients had less than six months of antimicrobial therapy [40], but this may relate to the fact that two patients died during treatment.

The date related to surgical treatment was also evaluated. Eleven patients underwent debridement and retention of the prosthesis (DAIR) [41], 38 had resection arthroplasty and reimplantation [42], while 13 patients had no surgical treatment [43].

Due to the scarcity of the data related to PJI caused by TB, we are unable to draw definitive recommendation for the antimicrobial treatment of surgical treatment for that matter. However, based on the recommendations of the World Health Organization (WHO) [44] for the treatment of osteomyelitis caused by drug-susceptible TB, we feel that the four drugs regimen (isoniazid (H) with pyridoxine, rifampin (R), pirazinamide (P) and ethambutol (E)) for two months followed by a two-drug regimen (rifampin (R) and isoniazid (H) with pyridoxine) for a total treatment duration of six to nine months (i.e., four to seven months two drugs) may be the most optimal management of PJI caused by drug-susceptible TB.

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QUESTION 6: Which antifungal agents are heat-stable and what dose of these agents should be used in cement spacers for fungal periprosthetic joint infection (PJI)?

RECOMMENDATION: Amphotericin B, preferably the liposomal formulation, and voriconazole are heat-stable antifungal agents that are available in powder form and can be added to polymethyl methacrylate (PMMA) cement for spacers during treatment of patients with fungal PJI. The optimal dose of the antifungals that need to be added to a spacer is not known. However, in the literature, the dose of amphotericin B ranges from 150 to 1,500 mg per 40 gm cement and the dose of voriconazole ranges from 200 to 1,000 mg per 40 gm cement. Antibiotics combined with antifungals should be considered for treatment/prevention of coexisting fungal and bacterial infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 92%, Disagree: 2%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Fungi are known to form biofilms on implant and tissue surfaces with associated tolerance to antifungal agents. Data on the antifungal concentrations needed to achieve the minimum biofilm eradication concentration (MBEC) is limited. Parenteral/systemic administration of antifungals can achieve minimum inhibitory concentration (MIC) but not MBEC, which is tens to hundreds of times higher than the MIC for most antifungal-pathogen pairs. Local delivery is therefore required for most cases, because it is expected that at a minimum, some biofilm fragments remain in the wound following debridement. The local delivery vehicle that is most commonly used is PMMA formed into a spacer. To incorporate sufficient antimicrobials for the required local release, the antimicrobial must be in powder form because sufficiently high concentrations are not currently available in solution form. Echinocandin antifungals (e.g., caspofungin and micafungin) are available in powder form and are water-soluble [1], but their heat stability is not established and there is limited data on release from PMMA [2]. 5-flucytosine is also available in powder form, but 5-flucytosine does not retain its bioactivity when incorporated into PMMA [3]. Amphotericin B and voriconazole are available in powder form [4–6]. Amphotericin B is heat-stable and voriconazole has limited heat degradation over the polymerization time for PMMA [7–9]. Both have release data available and are active when eluted from antifungal loaded bone cement [6,10,11]. However, neither amphotericin B nor voriconazole are water-soluble [12,13].

Amphotericin B is formulated with deoxycholate as a solubilizing agent. Liposomal formulations are also available in powder form and act to increase the release of amphotericin B from PMMA by an order of magnitude greater than amphotericin B deoxycholate. Eight hundred milligrams of liposomal amphotericin B (Ambisome®) per 40 gm of cement has been found to maximize amphotericin B release and not cause excessive mechanical weakness [10]. Toxicity studies are reported with cell injury in vitro, but no tissue injury in vivo at concentrations as high as 1,000 µg/mL [14]. Voriconazole is formulated with cyclodextrin as a solubilizing agent [15]. The cyclodextrin powder is 16 times the mass of voriconazole, resulting in a large enough powder volume to cause weakening of the cement [11]. Three hundred milligrams of voriconazole per 40 gm of cement leads to high levels of release, but also weakens compressive strength below the 70MPa ISO 5833 standard for normal implant fixation. When the dose is increased to 600 mg per 40 gm of cement, there is further weakening of compressive

TABLE 1. Summary of literature pertaining to the use of antifungal-loaded bone cement spacers

Year	Author	Antifungal	Dose (mg/40 gm cement)	Study Design	Follow-up (months)	# Infection Free (%)	Organism
2018	Burgo [17]	Voriconazole and vancomycin	Not reported	Case report	24	1 (100%)	*Trichosporon inkin*
2017	Daniele [18]	Voriconazole	V – 200	Case report	0	0 (0%)	*Scedosporium inflatum*
2016	Geng [15]	Amphotericin B +/- vancomycin +/- meropenem	A – 200	8 patients retrospective review	35-78	7 (87.5%)	6 Candida species, 1 *Aspergillus* 1 mold
2015	Wang [19]	Amphotericin B	A – 100	5 patients retrospective review	46	5 (100%)	Candida species in 4 cases and *Pichia anomala* in 1 case
2015	Ong [20]	Amphotericin B	A – 150	Case report	24	1 (100%)	*Arthrographis kalrae*
2015	MacLean [21]	Amphotericin B	A – 1500	Case report	24	1 (100%)	Blastomycoses
2014	Skedros [22]	Amphotericin B	A – 500	Case report	12	0 (0%)	*Candida glabrata* and S marcescens
2013	Reddy [23]	Amphotericin B	Not reported	Case report	24	1 (100%)	*Candida tropicalis*
2013	Deelstra [24]	Amphotericin B voriconazole	A – 250 V – 1,000	Case report	72	1 (100%)	*Candida albicans*
2013	Ueng [25]	Amphotericin B +/- vancomycin	Not reported	16 patients retrospective review	41	8 (50%)	9 C. albicans, 6 C. parapsilosis, 1 C. tropicalis
2012	Hwang [16]	**None** Spacers had 2 gm vancomycin/ batch No antifungal	Systemic	30 patients retrospective review	52	28 (93%)	24 were Candida species
2012	Hall [26]	Amphotericin B	A – 150	Case report	24	1 (100%)	*Aspergillus*
2012	Denes [27]	Voriconazole	V – 300	Case report	Not reported	Not reported	*Candida glabrata*
2011	Wu [28]	Amphotericin B	A – 1,200	Case report	12	1 (100%)	*Candida albicans*
2011	Gottesman-Yekutieli [29]	Itraconazole	I – 250	Case report	24	1 (100%)	*P. boydii*
2009	Wilkins [30]	Amphotericin B	Not reported	Case report	36	1 (100%)	Rhizopus
2009	Azzam [14]	Amphotericin B in 5 of 29 spacers	Not reported	29 patients retrospective review	45	9/19 (47%) reimplants	20 C. albicans, 4 C. parapsilosis, 3 C. albicans + *C. parapsilosis*, 3 non-Candida speies
2004	Gaston [31]	Amphotericin B + vancomycin	Not reported	Case report	9	0 (0%)	*Candida glabrata* amputation
2002	Phelan [32]	Fluconazole	F – 200	4 patients retrospective review	60.5	1 (25%)	Candida
2001	Marra [33]	Amphotericin B	A – 187.5	Case report	not reported	0 (0%)	*Candida albicans*

strength to about 20MPa after elution [11]. For spacer fabrication, some level of attention needs to be paid to structural integrity, and the use of metal reinforcement within the cement may help to minimize the risk of spacer fracture.

Currently, there is limited data on the local tissue levels needed, the duration of MBEC exposure required and the elution characteristics necessary to eradicate fungi from biofilm fragments. Clinical judgment must be used when choosing and dosing antifungal agents. The culture sensitivity in addition to the potential for antifungal toxicity must be weighed with the patient's medical history. Case reports and retrospective case series are valuable to consider in conjunction with the elution and mechanical data and the clinical factors specific to individual cases when dosing decisions are being made. Thorough debridement remains the foundation of PJI management, including fungal PJI. High-quality prospective clinical trials will be needed to determine clinical outcomes when local tissue level targets and thorough debridement are achieved.

Studies and case reports on the use of antifungal-loaded bone cement spacers are provided in Table 1. In these reports, amphotericin B and voriconazole were the dominant antifungals used in spacers with the dose of amphotericin B ranging from 150 to 1,500 mg per 40 gm cement and the dose of voriconazole ranging from 200 to 1,000 mg per 40 gm cement. Most report clinical success when used in conjunction with thorough debridement and systemic antifungals, however there are reports of acceptable outcomes even when antifungals were not used in any or all of the spacers [16–18].

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3.2. TREATMENT: MULTIDISCIPLINARY ISSUES

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QUESTION 1: Should periprosthetic joint infection (PJI) cases be referred to a regional center to improve the outcome of treatment and decrease cost?

RECOMMENDATION: Yes, for probable better outcome and greater efficiency.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 92%, Disagree: 6%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

PJI significantly increases the utilization of hospital and physician resources compared to primary cases or aseptic revisions [1]. There is evidence to support that primary total joint replacements performed in a specialized center may have lower complications and lower reoperations than those performed in non-specialized centers [2]. This experience should be extrapolated for the treatment of PJIs. It is reasonable to assume that treatment of patients with PJI in tertiary centers provides access to a multidisciplinary group of healthcare providers [3]. This is important, as management of patients with PJI usually requires interaction with a large group of healthcare providers such as infectious disease specialists, pharmacists, plastic surgeons, rehabilitation experts and so on. It has been demonstrated that the work of a multidisciplinary team using well-established protocols may achieve excellent results in management of a complex group of patients including those with PJI [4]. Moreover, an infected total knee arthroplasty (TKA) performed primarily at an arthroplasty center may have better clinical outcome after PJI treatment compared to those cases performed primarily in another type of hospital [5].

When treating a previously-failed PJI case, the place where the subsequent treatment is taken over may be even more important. A recent study evaluated the frequency, associated factors and mortality of amputation and arthrodesis after a failed treatment for infected TKA [6]. The results of this study suggest that recommending centers with a high volume of joint arthroplasties may be a way to reduce the risk of salvage procedures.

In agreement with our recommendations, it has been observed that referrals to tertiary centers to treat PJI have increased [7]. These cases may also generate a financial incentive for the accepting institution [7].

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QUESTION 2: What intraoperative findings during surgical management of orthopaedic infections need to be communicated with the infectious disease (ID) specialist?

RECOMMENDATION: Intraoperative findings that contribute to the diagnosis of periprosthetic joint infection (PJI) must be communicated to the ID specialist. The presence of a sinus tract (major diagnostic criteria) or any other valuable objective data such as cell count, neutrophil differential, frozen section, as well as the result of the point of care diagnostic tests, such as leukocyte esterase and lateral flow alpha-defensin need to be communicated to the ID specialist. The extent of infection, in terms of involvement of soft tissues and bone, any hardware retained and the antibiotic type and dose used in the cement spacer are also useful information that should be detailed in the operative report for communication with the ID specialist.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 90%, Disagree: 6%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

For the purposes of this review, information or data that could be obtained during the course of the surgery and that could impact or influence the surgeon's or infectious disease specialist's decision-making, were categorized into two groups: surgeon findings or observations and intraoperative tests. The recommendations below presume that the surgeon is already documenting/communicating the precise surgery performed (e.g., debridement with retention of prosthesis vs. resection arthroplasty vs. first-stage of two-stage revision) and any plans for future surgery.

The area with the least evidence to support recommendations was that of surgeon observations. Intraoperative findings observed by the surgeon that could impact the decision-making of either the surgeon or infectious disease specialist would seem to be reasonable information to relay to the ID specialist. However, the objectivity and standardization of these findings are highly variable. A prior study compared the clinical acumen of the orthopaedic surgeon to the addition of further advanced testing in diagnosing PJI and found that the addition of intraoperative visual inspection and histopathology improved the accuracy of the surgeon's preoperative diagnosis, though there was no description of discrete or objective definitions of the intraoperative visual inspection [1].

The presence of a sinus tract, one of the major diagnostic criteria of PJI, may be confirmed during the course of a surgery and should be relayed to the ID specialist [2]. The presence of purulence is one visual finding that had long been held as an important intraoperative finding that suggested infection [3] and was supported as a minor criteria in the definition of infection by the workgroup of the Musculoskeletal Infection Society (MSIS) [4]. Due to concerns about the subjectivity of the finding of purulence and the confusing picture that exists in the setting of other causes of cloudy synovial fluid, including metallosis and corrosion, purulence was removed from the minor diagnostic criteria by the International Consensus Meeting (ICM), when they revised the MSIS criteria. Alijanipour et al. [5] evaluated in their study whether purulence was a reliable marker of infection and found a sensitivity, specificity, positive and negative predictive values of 0.82, 0.32, 0.91 and 0.17, respectively. They noted that purulence was not correlated with higher culture positivity, but associated with higher synovial white blood cell (WBC) counts.

Recently, a publication by Parvizi et al. [6] entitled, "The 2018 Definition of Periprosthetic Hip and Knee Infection: An Evidence Based and Validated Criteria," established a diagnostic algorithm, emphasizing the role of intraoperative findings that are determinant for diagnosis of PJI. The recent criteria do include purulence as a minor criterion. The other tests have also been assessed using the preprobability testing and assigned a diagnostic score.

As the diagnosis of PJI is made usually by relying on a combination of tests, it is critical that the intraoperative findings related to its diagnosis are communicated with the ID specialist. For example, the presence of a sinus tract (major diagnostic criteria) should be confirmed intraoperatively and communicated to the ID specialist.

Other intraoperative findings that may also provide insight into the condition of the joint and influence treatment includes the soft tissue quality or condition, bone quality or condition, implant stability and the amount or type of hardware that was removed or retained. The ID specialists may alter the course and duration of the antibiotic treatment based on these findings. It is critical that the surgeon informs the ID specialist about any hardware that may have been retained. The latter, in particular, influences the course of treatment of the patient [7–10].

The second category of data that is obtained during the course of the procedure and should be communicated to the ID specialist are the results of intraoperative tests. If an intraoperative aspiration of the joint is performed and/or frozen section of the intraoperative samples are analyzed, the result of such findings should also be communicated to the ID specialist. These studies may impact the decision-making and help confirm the diagnosis. However, the results of these studies are not immediately available in the medical record or may not be recorded anywhere else, other than the surgeon's report. Intraoperative frozen histopathology represents one such study. Typical workflow entails a sample being sent to the pathology lab during the course of the surgery and often the result is telephoned into the surgical theater, with a formal written report to follow, sometimes days later. Given the potential importance of those findings on the decision-making and impact it may have on treatment [11–14], the results from this study should be communicated to the ID consultant. In addition to communicating the histology results, it is important to document the anatomic area from which the specimen was taken. Similarly, tissue samples sent for culture should be clearly labeled so that the ID specialist can understand which pathogens were found (e.g., superficial or deep, bone or synovium).

Other intraoperative tests may be valuable in the diagnosis and treatment decision-making for periprosthetic infections and the results should also be available to the ID consultant. Buttaro et al. [15] reported that synovial C-reactive protein (SCRP) had comparable diagnostic value compared to frozen sections. This was confirmed by Saleh et al. [16] who reported a high diagnostic value with SCRP, but also demonstrated diagnostic value testing for leukocyte esterase (LE), interleukin-6 (IL-6), interleukin-1ß, α defensin, and interleukin-17 biomarkers. Given the comparable findings in the literature combined with both the relatively inexpensive and immediate point of care (POC) results, Saleh et al. [16] recommend the use of LE testing as a first-line assessment when the diagnosis of PJI is questionable. Another POC test includes the lateral flow IL-6 device, which has shown promising results in the PJI population. Kasparek et al. [17] reported on a POC lateral flow test for α defensin and suggest that although it lacks the accuracy of the lab-based α defensin, it is comparable to evaluating frozen sections. However, they note that it has limited use in cases involving metallosis and further suggest that it may not be used in isolation to rule out PJI [17]. These findings were further supported by a recent review where the authors recommend that care must be taken when interpreting the results of the lateral flow α defensin test for the diagnosis of PJI intraoperatively [18]. As new POC tests are developed, or current ones are improved upon, the surgeon's intraoperative decision-making combined with these POC biomarker assays may prove to enhance the care that adult reconstruction patients are given, especially in the setting of revision total joint arthroplasty.

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QUESTION 3: What quality of life (QOL) measures should be used when determining the functional outcomes of periprosthetic joint infection (PJI) treatment?

RECOMMENDATION: Currently, there are no QOL measures specific to determining outcome in PJI. However, when determining the outcomes of any arthroplasty related procedure, the current recommendations are to use both a general well-being/QOL measure (i.e., Patient-Reported Outcomes Measurement Information System (PROMIS) Global 10, Short Form 36 (SF-36), the Veterans RAND 6-Item Health Survey (VR-12), EuroQol five-dimensional (EQ-5D)) and a joint/disease specific (i.e., Western Ontario McMaster Osteoarthritis Index (WOMAC), Hip Disability and Osteoarthritis Outcome Score (HOOS Jr) or Knee Injury and Osteoarthritis Outcome Score (KOOS Jr)) patient-reported outcome measure. Supplemental information such as surgeon-reported outcome measures, an activity-specific score and satisfaction surveys may be helpful. However, the ideal combination has yet to be determined and validated for patients treated for PJI.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 96%, Disagree: 1%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

One of the most severe complications after total joint arthroplasty (TJA) is a PJI [1]. Infections can present in many forms and their treatment can be just as variable (i.e., debridement, antibiotics and implant retention, one-stage exchange, two-stage exchange, resection arthroplasty, arthrodesis or amputation). Regardless of the approach, the goal of treatment is to improve the patient's overall and joint specific health. Outcome measures provide measurements of these domains to assess the effectiveness of an intervention [2]. However, there is no specific instrument of quality of life to evaluate patients with PJI at this time. Until such a tool is developed, the question becomes which of the existing measures should be applied to measure functional outcomes in this unique patient population.

After a literature review, 26 studies were identified from 1997 to 2017 that addressed functional outcomes in the setting of PJI treatments (Table 1). The most commonly-used outcome measurements were WOMAC (13 studies), Short Form 36 (SF-36) (10 studies), and Short Form 12 (SF-12) (10 studies). Overall, 19/26 studies (73.1%) reported both an overall health measure in combination with a joint or disease-specific measure. No studies compared one outcome measure to another as a gold standard outcome measure for TJA/PJI does not exist [2]. When compared to aseptic revisions, septic revisions tended to have worse functional outcomes [3,4] but differences in mental, emotional or satisfaction outcomes were mixed [3–6].

Since no current literature or consensus has specifically addressed which outcome measures should be used in infection, the recommendations are extrapolated from TJA in general. Meetings have recently been held to address the heterogeneity in outcome measure reporting in TJA in general. The first was the Patient-Reported Outcomes Summit for Total Joint Arthroplasty convened by the American Association of Hip and Knee Surgeons (AAHKS) in 2015 [7]. The group recommended that either the PROMIS 10 or the VR-12 instruments be used to assess general health, in addition to KOOS Jr and HOOS Jr for disease specific health. These instruments were chosen because they have been validated and contain a minimal number of questions [7–9]. This has been followed by The International Consortium for Health Outcome Measurements (ICHOM) as well as the International Society of Arthroplasty Registries (ISAR). Both have endorsed a multidimensional strategy in order to evaluate the results after TJA, including: (1) a general health/QOL score, (2) an organ-specific score and (3) a satisfaction question [10–12].

In conclusion, QOL outcome measures should be recorded in the PJI population similar to general arthroplasty. There is no evidence to suggest which specific outcome is superior in PJI patients as none

TABLE 1. Summary of PJI treatment studies using outcome measures

Author	Year	Outcome Measure	Design	Treatment
Younger [13]	1997	SF36, HHS, Satisfaction Questionnaire	Retrospective	Two-stage
Hsieh [14]	2004	WOMAC, HHS	Prospective	Two -stage
Wang [4]	2004	SF12, KSS	Prospective	Knee, two-stage
Meek [15]	2004	SF12, WOMAC, Oxford, Patient Satisfaction	Retrospective	Knee spacer
Klinger [16]	2006	SF36, KOOS	Retrospective	Knee, arthrodesis
Masri [17]	2007	WOMAC, HHS	Retrospective	Two-stage
Scharfenberger [18]	2007	SF36, WOMAC, HHS	Retrospective	Hip, two-stage
Parvizi [1]	2008	SF36	Retrospective	Two-stage
Cahill [5]	2008	SF36, WOMAC, Satisfaction Questionnaire	Prospective	Hip, knee
Biring [19]	2009	SF12, WOMAC, UCLA Activity Scale, Oxford 12, Satisfaction Questionnaire	Retrospective	Hip, two-stage
Romanò [6]	2010	SF12, WOMAC, HHS	Prospective	Hip, two-stage
Boettner [3]	2011	SF36, HHS	Retrospective	Hip
Leung [20]	2011	SF12, WOMAC, UCLA Activity Scale, Oxford, Satisfaction Questionnaire	Retrospective	Hip, two-stage
Kappler [21]	2012	SF12, WOMAC	Retrospective	Two-stage
van Diemen [22]	2013	HOOS, mHHS	Retrospective	Hip
Sabry [23]	2013	SF12, mHHS	Retrospective	Two-stage
Aboltins [24]	2013	HHS, SF12	Prospective	Hip, case control
Barbarić [25]	2014	SF36, WOMAC, COOP/WONCA, FES-I	Retrospective	Two-stage
Helwig [26]	2014	SF12	Retrospective	Hip, knee
Helito [27]	2015	SF36	Retrospective	Knee, amputation
Nuñez [28]	2015	SF36, WOMAC	Prospective	Knee, DAIR
Röhner [29]	2015	KOOS, SF36, WOMAC, KSS, Lysholm	Retrospective	Knee, arthrodesis
Aboltins [30]	2016	SF12	Prospective	Hip, DAIR
Grammatopoulos [31]	2017	OHS	Retrospective	Hip, DAIR
Poulsen [32]	2018	EQ-5D, OHS	Retrospective	Hip, two-stage
Beaupre [33]	2017	WOMAC, RAND 36	Retrospective	Hip spacer

SF36, Short Form 36; HHS, Harris Hip Score; WOMAC, Western Ontario McMaster Osteoarthritis Index; SF12, Short Form 12; KSS, Knee Society Score; UCLA Activity Score, University of California Los Angelos Activity Score; HOOS, Hip Disability and Osteoarthritis Outcome Score; Mhhs, Modified Harris Hip Score; COOP/WONCA, Dartmouth Primary Care Cooperative Research Network/World Organization of National Colleges, Academies, and Academic Associates of General Practitioners/Family Physicians; FES-I, Falls Efficacy Scale – International; KOOS, Knee Injury and Osteoarthritis Outcome Score; Lysholm, Lysholm Knee Score Scale; OHS, Oxford Hip Score; EQ-5D, EuroQol five-dimensional; RAND, Research and Development Corp.

of them have been specifically validated. Guidelines from previous meetings and consensus literature support the use of a both a global health measure in addition to a joint/disease specific measure at minimum, but do not specifically recommend a particular measure for PJI patients. Adjunct tools such as a satisfaction questionnaire should also be considered.

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Research Caveats

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QUESTION 1: Is there a distinct microbiome in the joints?

RECOMMENDATION: It remains unclear whether the native joint or a joint after arthroplasty can be considered a microbiological niche in which specific organisms reside without causing any manifestation of infection. However, given the innocuous character of microorganisms (such as coagulase-negative *Staphylococcus*, *Cutibacterium* species) recovered from clinical specimens in the context of aseptic loosening it appears plausible to hypothesize that chronic colonization of devices can occur and be of long-lasting nature before signs and symptoms of clinical infection occur, if they occur at all. Further studies are needed to determine the clinical relevance of microorganisms or microbial dysbiosis detected within joints, without apparent clinical features of infection, ensuring clinical correlation, long-term follow-up and multicenter validation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 80%, Disagree: 7%, Abstain: 13% (Super Majority, Strong Consensus)

RATIONALE

The term microbiome (or microbiota) is defined as the entity of microorganisms that colonize the human body. It is well-known that defined ecological niches (e.g., the gut, the skin, the oral cavity) can carry groups of microorganisms that differ dramatically in their specific composition [1,2]. There is growing evidence that the specific microbiome composition might be associated with defined clinical pictures or even support the development of illness, but without causing invasive disease [3].

However, in most cases the microbiome/microbiota would be considered to be beneficial for the host [4,5]. This commensal microbiome is expected to be found in niches of the human body traditionally regarded as non-sterile. In contrast, detection of commensal bacteria in sterile body sites (e.g., joints) would be regarded best as an artifact resulting from sample contamination or as evidence for a pathology evolving under certain predisposing conditions (e.g., immune suppression, foreign material implantation). Thus, in the current understanding, detection of single or multiple species originating from human microbiota in sterile body compartments would be primarily regarded as mono- or poly-microbial infection rather than as evidence for colonization. The physiologic or non-pathogenic presence of bacteria within the joint would therefore represent a groundbreaking change of current dogmas in microbiology.

In the face of these considerations, the general question under review comprises several distinct sub-questions: (1) Is there chronic microbial colonization in the joint, and can colonization occur without presence of foreign devices (i.e., an artificial niche)? (2) Can microorganisms establish chronic joint colonization without inducing infectious pathology or sequelae? (3) If so, are joints colonized by one or more species? (4) Can patterns of colonization be identified that predict defined clinical characteristics?

(1) Without doubt, there is chronic persistent colonization of joints in the presence of an implanted device. In fact, this is a basic characteristic of almost all infections caused by more innocuous (less virulent) organisms derived from the skin microbiota and able to form a biofilm [6]. There is limited data available as to which extent native joints also can also harbor such microorganisms. Evidence supporting this hypothesis comes from studies in which joint fluids from apparently uninfected individuals were microbiologically analyzed. Furthermore, some studies identified bacteria by culture or the strict protocols of molecular techniques from shoulder joint fluids [7–9]. Here, a relevant number of samples taken from patients without evidence for infection grew *C. acnes*. Unfortunately, in most of these studies it remains unclear if detection of *C. acnes* indeed represents colonization of the joint or rather was a consequence of contamination by skin flora due to insufficient skin washing procedures [10]. Moreover, since joint aspirates were performed for medical reasons, it is unclear if detection of bacteria would also be possible in individuals without any clinical evidence of infectious shoulder pathology.

(2) A hallmark of device-associated infection is a chronic persistent course with only low-grade inflammation. This course is most likely a direct consequence of biological traits related to microorganisms derived from resident skin microbiota – namely mechanisms that support persistence on the skin without inducing a relevant inflammatory response. In such a scenario, chronic colonization of foreign devices indeed could potentially occur through masking of the pathogen from effectors of the host immune system [11,12]. Some studies investigating explanted prosthetic devices from patients with periprosthetic joint infection (PJI) or aseptic loosening of a joint found small numbers of cases in which bacteria were unambiguously identified from the sample but that didn't show any sign of infection according to current standards (e.g., elevated C-reactive protein (CRP), elevated erythrocyte sedimentation rate (ESR), polymorphonuclear (PMN) cell tissue infiltration) [13–17]. However, of major importance, it is questionable if indeed such cases can be truly regarded as valid evidence for asymptomatic colonization of a device since assignment to the aseptic failure group is based on current algorithms to define PJI. While it remains open whether loosening of the implant can potentially be the only evident sign for an infection, it certainly is unclear if these patients would not have developed disease or PJI according to current case definitions if they remained untreated [18–20]. The relevant control group to test the hypothesis of chronic asymptomatic implant colonization has not yet been investigated, but would be completely asymptomatic patients with implants in situ. Importantly, in future investigations

and especially those applying molecular techniques strict protocols for sample processing, application of DNA-free consumables and process analysis (i.e., inhibitor controls) need to be applied.

(3) and (4) Building on the aspects discussed above, at present it remains unclear if the term "microbiome" is appropriate to describe microorganisms in native joints or after arthroplasty. Some evidence suggests, nevertheless, that more than one organism can potentially colonize artificial surfaces. It will be of major importance to unravel the extent of polymicrobial colonization and the potential importance of interspecies cooperation in future projects (making use of next-generation/metagenomic sequencing techniques and advanced microscopy methods [21]).

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QUESTION 2: Has the profile of organisms causing surgical site infection/periprosthetic joint infection (SSI/PJI) following orthopaedic procedures changed over recent years?

RECOMMENDATION: While the majority of organisms causing SSI/PJI continue to be staphylococcal species, the prevalence of resistant pathogens and atypical organisms continues to rise. In particular, incidence of methicillin-resistant *Staphylococcal aureus* (MRSA) is increasing. Isolated studies have reported an increased prevalence of culture-negative PJI. Further work regarding the flux in organism profile is needed, as it may confer significant antibiotic selection implications.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 5%, Abstain: 3% (Super Majority, Strong Consensus)

Data sources

Medline, Embase, Web of Science, Cochrane Library and reference lists of relevant studies from inception to February 10, 2018.

Selection criteria

Studies included were observational (prospective cohort, nested case-control or case-control, retrospective cohort) studies, case series and randomized controlled trials (RCTs) that have evaluated organism profile in PJI over time in patients undergoing orthopaedic procedures.

Review methods

Investigators screened and extracted data. We were not able to present a meta-analysis of the data. Thus, we present a narrative synthesis based on related data available.

Results

Of 113 potentially relevant citations, we found 23 relevant articles. Studies were observational and retrospective in design.

RATIONALE

Peersman et al. described that the predominant infectious organisms seen in 6,489 knee replacements were gram-positive (*Staphylococcus aureus, Staphylococcus epidermidis and Group B Streptococcus*) [1]. While current literature differs regarding specific percentages, there is consensus that gram-positive aerobic bacteria continue to remain the most common offending organisms [2–4].

In an aggregate of 14 studies examining 2,436 joints, *Staphylococcus aureus* represented 27% of all prosthetic joint infections, coagulase-negative *Staphylococcus* represented 27%, *Streptococcus* species were represented at 8%, *Enterococcus* species were represented at 3%, aerobic gram-negative bacilli made up 9%, anaerobic bacteria comprised 4%, culture-negative PJI was responsible for 14% and polymicrobial infection represented 15% [3–18]. In a study analyzing organism profile at 2 separate referral centers, *Staphylococcus aureus* remained the most prominent offending organism at 26.9% of cases [19]. Additional studies are congruent with the findings reported by by Aggarwal et al. [2,19–21].

However, prevalence of resistant organisms continues to increase. In 2005, Ip et al. described a retrospective case series in which they described the bacterial isolates from 1995 to 2003 [22]. They noted that no isolates from 1995 and 1996 were multiple-drug resistant, a change observed in the later years [22]. McLawhorn et al. showed MRSA and methicillin-susceptible *S. epidermidis* (MRSE) combined to account for 18.1% of PJI pathogens in the United States [23]. Interestingly, a study analyzing prevalence of causative organisms at two separate tertiary centers showed methicillin resistance as significantly more common in the US than in Europe [19].

In summary, the mainstay of organisms causing SSI/PJI continue to be staphylococcal. The prevalence of resistant pathogens and atypical organisms also continues to rise. The prevalence of methicillin-resistant *Staphylococus aureus* and culture-negative infection is also increasing. Further work regarding SSI/PJI organism profile is needed, as it may confer significant antibiotic selection implications.

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QUESTION 3: What methods can the Food and Drug Administration (FDA) and other regulatory bodies use to evaluate the efficacy of novel anti-infective technologies?

RECOMMENDATION: The FDA and other regulatory bodies can use in vitro cell culture methods to evaluate the antimicrobial efficacy against pathogens, followed by animal studies to evaluate osseointegration issues and a subsequent osteomyelitis/periprosthetic joint infection (PJI) animal model to evaluate the in vivo efficacy. However, clinical trials may be required for clearance or approval of some novel anti-infective technologies.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 80%, Disagree: 3%, Abstain: 17% (Super Majority, Strong Consensus)

RATIONALE

Human clinical trials of anti-infective technologies are inherently difficult to perform according to Lazzarini et al. [1], due to the low incidence of implant-associated infections, the heterogeneous patient population, various treatment options in arthroplasty, the surrounding tissue condition after debridement and the broad range of causative pathogens and associated virulence patterns [2]. A cascade of in vitro cell culture methods and especially meaningful experimental animal models have to serve to fill this inevitable gap [1].

During the development of anti-infective biomaterials and devices and the determination of their anti-microbial properties, reliable in vitro test methods are essential to characterize implant surfaces [1,3]. In any evaluation procedure, cell proliferation has to be included as an important step in the course of infection [3]. For appropriate anti-microbial efficacy testing the independent aspects adhesion, proliferation and detection of bactericidal activity shall be considered in a consistent approach [3,4].

In the almost identical anti-microbial test methods, described with Japanese Industrial Standard (JIS) Z 2801:2010 and the International Organization for Standardization (ISO) 22196:2011 standards, the bacteria are applied onto the sample surface and covered under a sterile film, whereas for the American Society for Testing and Materials (ASTM) E 2180 test method the bacteria are applied as a thin agar slurry film. After 24 hours, by recovering vital bacteria from the samples, both test methods' anti-microbial efficacy is determined as the difference between the untreated reference and the anti-microbial sample. The major limitations are the required sample size (ISO 22196 5 x 5 cm, ASTM 3 x 3 cm) and the flat and smooth surface geometry, which is often not a given for orthopaedic implants [4]. In addition, hydrophobic surfaces can be unsuitable for testing according to ISO 22196, and the applied agar film (ASTM E 2180) can be too thick for non-leaching surface bound anti-microbials, thus leading to false-negative results.

Proliferation assay-based methods, first described by Bechert et al. [3], measure the antimicrobial efficacy based on the reproduction and release of daughter cells, monitoring the growth activity of these offspring bacteria over time. The main advantage of the proliferation-based assays is a broad applicability to flexible sample geometries (e.g., 2D and 3D), surface properties (e.g., smooth, textured, porous) and test conditions (e.g., leaching and non-leaching) [3–5]. Moreover, this method allows a parallelized investigation of many different setups in one test run ensuring a direct comparability, which results in increased explanatory power and higher sensitivity as given in the ISO and ASTM test methods [3,4]. However, the interpretation of test results is somehow more sophisticated, since growth of the offspring bacteria is analyzed rather than the vital cells on the sample surface [3,4]. In case of more complex surface structures and 3D geometries, which is the case for orthopaedic implants, the most reliable test method is a proliferation-based assay [4]. An important additional aspect is the contact of the implant to body fluids (such as blood, serum or interstitial liquid), having typically a high concentration of proteins, covering the device surface by a protein layer, which can have an impact on the antimicrobial performance of the material. Moreover, the influence of sterilization, aging degradation and persistence of the anti-microbial effect should be examined and testing should always be performed at least against gram-positive and gram-negative bacteria strains [4]. However, a direct transferability of in vitro results to in vivo performance is not stringently given. Thus, animal data are required to substantiate the antimicrobial efficacy in vivo.

To demonstrate unimpaired osseointegration for implant materials and surfaces that are modified by new anti-infective technologies in hip and knee arthroplasty, an appropriate animal study should be performed using controls based on long-term, clinically-established implant surfaces for cementless fixation, and also the base material and surface structure without the anti-infective treatment. Eto et al. [6] described a rat model with intramedullary implantation of a titanium rod to evaluate the osteoconductivity and osteogenesis in the meta- and diaphyseal region of the distal femur for experimental silver-oxide-containing hydroxyapatide coatings. They examined the implant anchorage strength at 2, 4 and 12 weeks post-implantation in a pull-out test, and performed a histological examination using a contralateral femur implantation with the same surface [6]. Analyzing the surface coverage with bone, they used this procedure to quantify the active peri-implant osteogenesis and osteoconductivity in the meta- and diaphysis of the femur in a comparison of anti-microbial surface treatments to a clinically-established hydroxyapatite (HA) coating [6]. Combining biomechanical and histological examinations, the model by Eto et al. [6] is valuable during the development phase of new anti-microbial implant surfaces to detect favorable solutions. The limitations of size, not allowing for testing multiple implants simultaneously and also significant dissimilarities between rat and human bone make a rat model unsuitable for clinically relevant osseo-integration testing [7].

To evaluate new anti-microbial surface solutions for a clinical use in orthopaedic implants, their biocompatibility, peri-implant osteogenesis, osteoconductivity and ability of osseointegration should be tested in an animal model of a higher species, like sheep, goat, pig or dog [7,8]. Preferably a load-bearing model of the proximal tibia or distal femur in direct implantation site, or autologous left-right comparison should be performed, in reference to a clinically established surface (e.g., HA or porous coating) under a mid-term implantation duration of at least 26 weeks, to evaluate the osseointegration in a substantiated manner [7–10].

Animal models with osteomyelitis have been used previously to investigate potential treatment options using implants. After a review of the existing literature, it was found that a wide variety of osteomyelitis animal models exist [9]. However, no ideal single animal model exists to address implant associated osteomyelitis. Therefore, we propose that researchers and clinicians should ask indication and disease-specific questions and build on established appropriate animal models capable of answering their questions and enabling translations to the clinical situation [9]. Traditional methods to quantify bacterial load via colony forming unit (CFU) assays should be replaced with in vivo bio-luminescent imaging and radiological outcome quantification. New anti-microbial treatments should be evaluated in regard to the host immune response utilizing biomarkers, and shoud be based on new technologies like the detection of bacteria by fluorescent in-situ hybridization in bone infection [9,11].

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QUESTION 4: What are some of the emerging pre-clinical methods for evaluating novel antimicrobial technologies?

RECOMMENDATION: At present, most in vitro testing provides limited insight into the potential of novel antimicrobial technologies. More recently, in vitro models that incorporate animal or human tissue are emerging to test adherence and colonization to devices in contact with human tissues. Further development and validation of these models is needed, as well as approaches to include the element of human immune response.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 81%, Disagree: 2%, Abstain: 17% (Super Majority, Strong Consensus)

RATIONALE

The Food and Drug Administration (FDA) held a workshop in 2014 on antimicrobial/antibiofilm technologies and has published a white paper on the workshop outcomes [1] as well as a book chapter in 2016 [2]. The FDA recognizes the public health impact of medical device associated infections including prosthetic joint infections. There are two types of pre-clinical antimicrobial effectiveness testing: in vitro and in vivo. In this response, in vitro testing is addressed.

In Vitro Testing

At present, most in vitro testing provides limited insight into the potential of novel antimicrobial technologies. Most Clinical and Laboratory Standards Institute (CLSI) and United States Pharmacopeia (USP) tests (e.g., CLSI M02-A11, CLSI M07-A9 and USP 51) are for planktonic bacteria and/or are not ideal for medical device technologies. Some of the newer American Society for Testing and Materials (ASTM) methods are focused on creation of reproducible microbial biofilms for testing, but are not specifically developed with methods and endpoints that are appropriate for medical devices. Medical devices have a range of patient contact types (e.g., indwelling, transcutaneous and implanted) and duration (e.g., prolonged vs. permanent contact). A notable consideration for permanent contact implants is how to identify an effective dose that can prevent biofilm formation where multiple applications of the antimicrobial are not feasible). Therefore, modification and careful development of protocols to demonstrate in vitro effectiveness is necessary for specific medical device applications.

Differences based on material properties are more easily detected in adhesion studies since they are typically conducted using short times while in saline, where bacterial growth is minimal. Thus, adhesion testing is better suited for comparing early stage bacterial interactions with different antimicrobial technologies or libraries of materials. The ASTM E2647 drip flow reactor or similar type flow systems have been used to study early stage bacterial adhesion and biofilm formation [3,4]. An alternative approach to adhesion testing is to put samples in microtiter plates with an orbital incubator and to extract colonies after testing the antimicrobial strategy [5]. While this approach is simpler to set up and does not require sophisticated and costly confocal microscopy equipment to visualize cells, it is an endpoint method rather than a real-time approach. There may also be limitations due to the extraction technique employed and the presence of viable but non-culturable (VBNC) bacteria. When testing adhesion, one should keep in mind that surfaces which initially repel bacteria may fail after some period of time due to buildup on the surface, fouling by dead bacteria and interactions with bodily fluid and tissues.

For longer-term biofilm testing, the ASTM E2562 CDC flow reactor is a lab-scale model suitable for testing coupons from medical devices or entire small devices [6]. It has been used extensively in the literature for testing antimicrobial device technologies. A limitation of this approach is that bacteria are typically provided continuous nutrients so that a mature and fully-saturated biofilm is achieved. This can reduce the sensitivity for comparing between similar materials with slight differences, such as different types of patterned/textured surfaces. The ASTM E2799 minimum biofilm eradication concentration (MBEC) assay is a higher throughput format than the CDC reactor, but requires modification to be used with medical devices [7]. It is challenging to perform successfully due to the number of steps and requires significant work to optimize for each material and strain.

Two promising in vitro approaches that have the potential to increase realism in testing are human cell-based co-culture and ex vivo tissue models. Bacterial co-culture with human cells is challenging and its use for testing is still in experimental development. It can include human tissue cells [8] and/or human immune cells [9]. A more achievable approach at this time is ex vivo tissue-based models. The use of ex vivo porcine skin explants has shown great promise as a tool to study the development of more mature biofilms with greater resistance to antimicrobials [9–11]. The next logical step is the use of human tissue models such as a recent article showing how the use of human epithelial tissues has yielded valuable information on the fitness of bacteria to adhere to and colonize human

cells [12]. Such models could potentially allow for simulation of the tissues in contact with an orthopaedic implant for evaluation of anti-biofilm stratgies.

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QUESTION 5: Does an animal model for periprosthetic joint infection (PJI) exist?

RECOMMENDATION: Yes, there are several animal models using different species and implant designs that have claimed to pertain to PJI. However, the majority of these models are not representative of clinical PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 88%, Disagree: 4%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

Despite its increasing prevalence, our fundamental understanding of how bacteria enter the human prosthetic joint, establish biofilm, resist immune response and overcome clinical treatment remains limited. Establishing representative animal models of human disease has led to translational breakthroughs in medical fields such as immunology [1], toxicology [2], oncology [3] and orthopaedics specifically have led to the introduction of novel therapies such as for fracture healing [4] and for improved osseointegration surfaces [5] in joint reconstruction. With such examples, it is conceivable that a clinically representative animal model of PJI could improve our understanding of the pathogenesis of PJI and consequently lead to novel strategies for PJI prevention and treatment.

A systematic review of the literature was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify published animal models described to be representative of PJI. The majority were in mice (14) [6–19], with rabbit (5) [20–24], rat (2) [25,26], sheep or ovine (2) [27,28] and dog or canine (1) [29] comprising the species utilized. Utilizing large-animal models such as dogs and sheep permit more frequent serum analyses and involve bony architecture that contains osteons and Haversian systems, which are similar to human bone [30]. However, larger animals have more porous bone that turns over more rapidly compared to humans, making metrics such as osseointegration and osteolysis more difficult to interpret [31]. Smaller animal models are advantageous due to their substantially lower-running costs and, uniquely thus far in the case of mice, the possibility of genetic manipulation to reproduce human disease states [32,33]. However, rodent immune systems are mostly rich in lymphocytes, a stark difference from the largely neutrophil-based immune response found in humans [34]. There currently is no consensus on which animal species is ideal for modeling PJI.

The majority of studies failed to utilize implants that effectively recreate the periprosthetic environment, characterized by the implant separating the articular space from the intramedullary space, or that bear load. The most popular choice was a stainless steel wire inserted retrograde into the femoral canal [6–9,11–13,16–18,24–26,35,36], an implant which does not bear load, is not of the same material as arthroplasty implants, is mechanically loose and fails to recreate the periprosthetic space. The second most popular choice was a titanium screw (with or without a washer) placed across the proximal tibial cortex [14,15,23,28,37], an implant which bears load and uses a correct arthroplasty material, but does not involve the medullary canal and preserves articular cartilage. Three articles utilized implants that bore weight and separated the articular and medullary spaces [19,21,22]. However, two of these articles utilized a silicone implant [21,22] and only one utilized the correct titanium alloy used in clinical arthroplasty implants [19]. This latter example was the only model that fulfilled implant-related criteria. Troublingly, two articles made cortical bone windows and utilized no metal or plastic-based implants whatsoever [10,20].

Almost all studies (23) involved gram-positive organisms including methicillin-sensitive *Staphylococcus aureus* (MSSA) [7–9,11–21,24,25,28], methicillin-resistant *Staphylococcus aureus* (MRSA) [6,22,23,26], and *Staphylococcus epidermidis* [10]. All bacteria utilized in retrieved studies were commercially available strains. There is incomplete information pertaining to the biofilm-forming ability of these strains and, to our knowledge, no study used bacteria derived directly from clinical PJI. The most common method of bacterial inoc-

ulation involved injecting bacteria into the articular space following implant insertion and wound closure [7–9,11,12,16,17,21–23,26,28]. Alternatives that share clinical relevance included injecting bacteria into the medullary canal prior to implant insertion [10,18,20,24], pipetting bacteria onto the implant immediately after insertion [6], and administering bacteria intravenously [13,25]. Another method which is not clinically representative is to culture the implant in bacterial broth for 24 hours, permitting biofilm to form on the surface prior to insertion [14,15].

Methodology to determine bacterial viability varied across the retrieved articles, but was not restricted to model type. More comprehensive analyses were identified in mouse-based studies, with biofilm architecture, bacterial colony counting on tissues and implant surfaces and descriptions of immune responses being collectively described in several studies. To date, no non-mouse based study has included quantitative measurements of bacteria, biofilm, and host immune response.

Mouse-based models of PJI are currently the most popular and provide the most comprehensive methodology for PJI-related investigations. Unfortunately, the majority of these models fail to utilize implants that function like their clinical counterparts. This finding is disappointing considering the successful animal models available in orthopaedics for trauma [38] and sports-related conditions [39].

Although intramedullary pins remain popular in PJI-themed models, they have obvious deficiencies when trying to represent arthroplasty components and have been confused in representing osteomyelitis and septic arthritis [10,15]. Carli et al. proposed four criteria that all animal models of PJI should meet: (1) modeling should be performed in animals with comparable musculoskeletal and immunological properties to humans, (2) utilized implants should be of clinically relevant materials, (3) models should use clinically relatable bacteria that can form biofilms on implant surfaces and (4) methodology should include quantitative measurements of bacteria, biofilm and host immune response [40]. One animal model [19] currently fulfills this criteria. Unfortunately, this model has only recently been introduced and requires further validation with the testing of prophylactic or therapeutic PJI investigations.

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QUESTION 6: Are there any concerns regarding the use of joint registries or administrative databases to conduct infection studies?

RECOMMENDATION: Yes. Infections are of a multi-factorial character and currently, national joint registries alone do not provide adequate data for a comprehensive approach to infection research.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 91%, Disagree: 6%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

National joint registries are platforms for aggregating various data on surgical procedures and their subsequent outcomes. The data can be used for further research and also as a means of direct feedback to contributing clinicians via the annual reports.

The systematic review performed generated 19 articles conducting infection research using a national joint registry alone. The utilization of national registries enables a nationwide study setting with large populations. Analyses of these large study sets can identify trends of statistical significance of which further research may be targeted. The 19 identified articles examine various aspects of infection. Three articles have investigated the incidence of infection over time and indicated that the incidence of prosthetic joint infection (PJI) has increased [1–3]. Registry datasets have also been used to study the risk of revision secondary to infection, the burden of revision due to infection and the risk factors for infection in primary arthroplasty [4–9]. Other studies have evaluated prosthetic components and intraoperative details with regards to infection risk [10–16]. One study reported on the of risk re-revision in four different surgical procedures used to treat infection [17].

The annual reports and data collection forms available on the websites of eight established national joint registries were reviewed [18]. It appears that reporting on infections varies between the registries [19–28]. Further, the definition of infection is inconsistent in the registries, and there is no distinction between superficial infections and deep periprosthetic infections. Patients with infections who were not subject to revision or other reoperations are not captured within these databases. Some registries report infection as revision procedures for infection, defined as all procedures manipulating, exchanging or removing prosthesis parts [21–23]. Other registries report on all open procedures, regardless of exchange, addition or removal of implant components [19,20,24,25]. The remaining categorize procedures due to infection in their own manner [26–28].

It could be argued that with infections being of a multi-factorial nature, the data collected in the registries alone is not sufficient enough to conduct comprehensive infection-based research (Appendix A). With a few exceptions (e.g., Swedish Knee Arthroplasty Register), there is no information on factors such as causative pathogen or antibiotic regime. However, this information can be obtained by performing linkage studies with several registries, such as joint, microbiological and drug registries. In Denmark, Sweden, and Finland, such studies have been conducted to investigate PJI [29–33]. Using a linkage of databases, Gundtoft et al. found a 40% higher incidence of infection after total hip arthroplasty (THA) than registries have previously reported alone [29]. In Sweden, Lindgren et al. reported on a method to investigate the incidence of infection by linking the national drug registry with the national hip joint registry [33]. Holleyman et al. have also used a combination of the National Joint Registry database for England and Wales (NJR) and a register on microbiology data to study which microbes cause PJI [34,35]. Also in Sweden, the Knee Arthroplasty Register conducted a study where data on microbiology and antibiotics was requested from centers for the included patients. The study found that there was a 75% success rate after debridement, exchange of tibial insert and antibiotics in infected total knee arthroplasty (TKA) [36].

Different registries vary in how they report, define and analyze infection rates in their annual reports; thereby making it difficult to conduct a representative comparison across the registry websites. Similar to revision burden being used as a means of comparing registries, Springer et al. used annual reports from six national arthroplasty registries to investigate the infection burden in each registry [3]. Infection burden has been concluded to be a possible way of comparing the success between registries. However, the inconsistency in data collection and definition in the annual reports throughout the registries make it problematic to compare and interpret infection within registries. Additionally, infection burden has been suggested to be underestimated in national joint registries [37–39].

Jämsen et al. conducted a study to estimate the rate of infection following TKA in Finland and came to the conclusion that the incidence of revision TKA secondary to infection seemed to be underestimated [37]. Two studies of the national joint registry in New Zealand came to the same conclusion [38,39]. The registries report

on completeness of registered data in their annual reports but do not specifically report on the completeness of reported infection procedures. Validation of data reported on infection to the registries is important in order to maintain a high data quality within these databases. To our knowledge, validation studies on infection have also been conducted within the Danish and Swedish national joint registries [40,41].

Although there are limitations, we believe that registries will play an important role in future infection research. A harmonization of infection definition and data collection is desirable. We also believe collaborative research linking data from national joint, national drug and microbiological registries will provide a more comprehensive approach to infection research.

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APPENDIX A. Variables Collected By Major Arthroplasty Registers

VARIABLE	HIPS							
	AUS	CAN	DEN*	NJR	NEW**	NOR	SWE	FIN
Sex	X	X	X	X	X	X	X	X
Age	X	X	X	X	X	X	X	X
ASA	X			X	X	X	X	X
Other comorb. Score								
Height	X			X	X		X	X
Weight	X			X	X		X	X
Hospital	X	X	X	X		X	X	X
Surgeon	X	X		X		X	X	X
Date	X	X	X	X	X	X	X	X
Previous hip surgery			X			X		X
Primary diagnosis	X	X	X	X	X	X	X	X
Primary procedure details	X	X	X	X	X	X	X	X
Laterality	X	X	X	X		X	X	X
Revision diagnosis	X	X	X	X	X	X	X	X
Type of procedure			X	X		X	X	X
Surgical Approach	X		X		X	X	X	X
Patient positioning				X		X		
MIS						X		
Implant details	X	X	X	X	X	X	X	X
Type of fixation	X	X	X	X	X	X	X	X
Fixation details		X	X	X				
Charnley class							X	
Type of OR			X		X	X		
OR attire			X					
Operative time			X		X	X		X
Perioperative complication				X		X		X
Navigation/Robotics	X							
Bone Loss			X			X		
Trochanteric osteotomy			X	X		X		
Image derived instrumentation	X							
Functional group			X					
Harris Hip Score			X					
Antibiotic prophylaxis			X		X			X
Thrombosis prophylaxis			X	X				X
Type of anaesthesia			X	X				X
Drainage use								X
Bone transplantation				X	X			
Surgeon experience				X	X			X

*Not available on website, but summarized on Danish Orthopaedic Common Database (DOF).

**Not available on website, based on annual reports.

VARIABLE	KNEES							
	AUS	CAN	DEN*	NJR	NEW**	NOR	SWE	FIN
Sex	X	X	X	X	X	X	X	X
Age	X	X	X	X	X	X	X	X
ASA	X			X	X	X	X	X
Other comorb. score								
Height	X			X	X		X	X
Weight	X		X	X	X		X	X
Hospital	X	X	X	X		X	X	X
Surgeon	X	X		X		X	X	X
Date	X	X	X	X	X	X	X	X
Previous knee surgery			X			X	X	
Primary Diagnosis	X	X	X	X	X	X	X	X
Primary procedure details	X	X		X	X	X	X	X
Knee score			X					
Functional group			X					
Laterality	X	X	X	X		X	X	X
Revision diagnosis	X	X	X	X	X	X	X	X
Type of reoperation			X	X		X	X	
Surgical approach	X		X	X	X	X		X
Bloodlessness			X				X	
Positioning						X		
MIS						X	X	
Implant details	X	X	X	X	X	X	X	X
Type of fixation	X	X	X	X		X	X	X
Fixation details		X	X	X			X	X
Type of Operating Room			X		X	X		
Operation time						X	X	X
Perioperative complication			X	X		X		X
Navigation/Robotics	X						X	
Bone loss						X		
Image derived instrumentation	X							
Patella component	X			X				
Spacer use	X							
Bone transplantations			X	X				
Thrombo-prophylaxis				X			X	X
Local infiltration analgesia							X	
Drainage use							X	X
Peroperative antibiotics							X	X
Surgeon experience				X				X
Type of anaesthesia				X			X	X
Patient specific instruments				X				

*Not available on website, but summarized on DOF.

**Not available on website, based on annual reports.

PART II

HIP AND KNEE

Continued...

Prevention

1.1. PREVENTION: HOST RELATED

Authors: Richard Iorio, Zlatan Cizmic, James E. Feng, Setor Kunustor

QUESTION 1: What are the absolute and relative contraindications to elective primary total joint arthroplasty (TJA), with respect to surgical site infection (SSI) and periprosthetic joint infection (PJI) risk?

RECOMMENDATION: Elective joint arthroplasty is contraindicated in patients with an infectious lesion in the ipsilateral extremity, until the infection is resolved. TJA needs to be deferred in patients with uncontrolled conditions such as diabetes, malnutrition, chronic kidney disease, as well as other diseases that are known to increase the risks of SSIs/PJIs.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 90%, Disagree: 7%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Immunosuppression and Rheumatoid Arthritis (RA) (Relative Modifiable Risk Factors (MRF))

Evidence Strength: Moderate

Current studies evaluating the risks of PJIs in immunosuppressed patients have primarily been grounded in transplant patients (discussed in later sections), and those receiving biologics or non-biologic disease modifying anti-rheumatic drugs (DMARDs). In a Japanese study by Momohara et al., the risk for post-TJA SSI due to biologic DMARDs was compared against that of non-biologic DMARDs in RA patients [1]. Of note, non-biologic DMARDs were continued throughout the perioperative period, but biologic DMARDs were withheld in concordance with the British Society for Rheumatology and Japanese College of Rheumatology guidelines (~2 to 4 weeks based on half-life). The odds ratio (OR) for SSIs with biologic DMARDs was 5.69 (95% confidence interval (CI) 2.07-15.61). Furthermore, multiple logistic regression analysis found tumor necrosis factor-α blocker therapy to be the most potent of the biologics, with infliximab conferring a 9.8 greater odds (OR 2.41-39.82) and etanercept conferring 9.16 greater odds (95% CI 2.77-30.25) for SSIs. The only other significant risk factor for increased SSIs was RA disease duration (OR 14.5; 95% CI 8.9–21.0). A separate Japanese hospital surveillance study also demonstrated a smaller, but significant increase in SSIs with biologic DMARDs when compared to non-biologic DMARDs (OR 2.12; 95% CI 1.48–3.03) [2].

Conversely, a Danish database study comparing biologic versus non-biologic DMARD treated TJA candidates found no significant differences in PJI rates (adjusted hazards ratio 1.61; 95% CI 0.70-3.69) [3]. Furthermore, glucocorticoid exposure within 90-days of surgery was found to increase the 1-year risk for PJIs (OR 2.31; 95% CI 1.09 to 4.89). Lastly, one-year PJI risk was also elevated in RA patients when compared to osteoarthritis patients (OR 1.59; 95% CI 1.23-2.04).

The American College of Rheumatology (ACR) and American College of Hip and Knee Surgeons (AAHKS) have recently developed guidelines with regards to biologic and non-biologic drug management in the perioperative period [4]. Current guidelines indicate biologic DMARDs are to be discontinued in the perioperative period based on medication half-lifes. However, discontinuation may still not deter the risks conferred. In general, traditional, nonbiologic DMARDs can be continued throughout the perioperative period.

Intra-articular Injections (Modifiable)

Evidence Strength: Strong

In a matched cohort database study by Cancienne et al., patients receiving intra-articular corticosteroid injections of the knee were separated into three cohorts based on the last injection prior to surgery: 0 to 3 months, 3 to 6 months and 6 to 12 months. Matched controls were selected based on the absence of any previous intra-articular injections. Patients receiving intra-articular steroids 0 to 3 months before surgery demonstrated an increased risk for infection at 3 months (OR 2.0; 95% CI 1.6-2.5; 2.60% vs. 1.33%) and 6 months (OR 1.5; 95% CI 1.2-1.8; 3.41% vs. 2.34%) postoperatively. For patients receiving corticosteroids more than 3 months preoperatively, no increase in postoperative PJI was observed. A similar database study of 173,958 THAs by Schairer et al. showed intra-articular corticosteroid injections 0 to 3 months preoperatively increased the risk of infection 0 to 3 months (Hazard Ratio (HR) 1.52), 3 to 6 months (HR 1.46) and 6 to 12 months (HR 1.39) postoperatively [5]. Similar to the findings from Cacienne et al., it was reported that steroids injected greater than three months preoperatively did not increase postoperative PJI risks.

The quantity of intra-articular steroid injections within one year of surgery may also play a role in PJIs. Chambers et al. reported increased infection rates in patients who received two or more intra-articular steroid injections (OR 3.30; 2.0% vs. 6.6%) when compared to those who only received one. Like the studies performed by Cancienne et al. and Schairer et al., viscosupplementation patients were excluded from the study.

Current systematic reviews and meta-analyses have attempted to better define the effects of intra-articular injections, but a paucity of prospective studies, randomized-control trials and highly variable study designs have led to highly confounded and poorly defined results [6–9]. Moreover, with PJI rates of approximately 3% in total knee arthroplasty (TKA) [10] and 0.4-2.2% in total hip arthroplasty (THA) [11,12], current studies are reported to be too underpowered to detect the differences in PJI rates.

There is strong evidence that surgery should be absolutely delayed for a minimum of three months following intra-articular steroid injections. Surgeons may also consider intra-articular injections of the knee within three months to one year a potential relative contraindication. However, future large cohort or randomized control trials are required to assess the true risks. Evidence regarding viscosupplementation is unavailable.

Body Mass Index (BMI) ≤ 20 (Modifiable)

Evidence Strength: Moderate

In a case-control study of 27 patients by Manrique et al., underweight patients (BMI <18.5 kg/m^2) suffered from an increased risk for SSIs (11.1% vs. 0.0%). Conversely, in a database study of 4,665 TJAs by Anoushiravani et al., patients who are underweight (BMI ≤ 19 kg/m^2) were at reduced risks for PJIs (OR 0.23; 95% CI 0.09-0.61) [13]. Similarly, when underweight patients were compared to obese patients, no differences in infection rates were observed [14]. Current evidence for or against PJIs in underweight patients are equivocal; however, due to the multitude of complications associated with underweight patients, TJA is relatively contraindicated, and medical optimization should precede TJA.

Obesity (Modifiable)

Evidence Strength: Strong

In a retrospective database study by Werner et al., postoperative outcomes of 891,567 patients undergoing THA were stratified into four distinct cohorts: non-obese (BMI < 30 kg/m^2), obese (BMI 30-40 kg/m^2), morbidly obese (BMI 40-50 kg/m^2) and super-obese (BMI > 50 kg/m^2) [15]. The risks of SSIs increased with increasing BMI. SSI rates were noted to be 0.8% in the non-obese, 2.6% in the obese, 5.2% in the morbidly obese and 12.4% in the super-obese. In a study of 71,599 cases by Fu et al., wound complications (superficial infections, deep surgical site infections, organ space surgical site infections or wound dehiscences) were also observed to positively correlate with BMI, with 0.8% of non-obese patients experiencing wound complications, 0.9% in class 1 obesity, 1.0% in class 2 obesity and 1.7% in class 3 obesity [16]. In addition, patients diagnosed with malnutrition were two times more likely to have wound complications (2.0% vs. 1.0%). Hypothyroidism should also be evaluated in this population, as new studies indicate a potential causal link between the two disease states and PJI [17,18]. These findings of increased SSIs with obesity have been supported by several meta-analyses [19–21]. Current management guidelines indicate weight loss is helpful in reducing PJIs in this patient population. Hence, obesity is considered a relative contraindication while morbid obesity serves as an absolute contraindication. However, the current approach to weight loss protocols is highly controversial, with no absolute guidelines for which methodology (e.g., diet/exercise vs. medically prescribed very low-calorie diets vs. bariatric surgery) is superior.

Bariatric Surgery (Non-modifiable)

Evidence Strength: Strong

Studies regarding the effect of pre-TJA bariatric surgery remain equivocal. In a matched cohort study by Inacio et al., bariatric surgery did not result in significantly lower rates of 1-year deep or 30-day superficial infections when compared among patients with bariatric surgery > 2 years prior to TJA (superficial 0%; deep 1.5%), those with bariatric surgery within 2 years of TJA (superficial 2.0%; deep 1.0%) and obese patients without bariatric surgery (superficial 1.2%; deep 0.5%) [22]. In a study by Watts et al., bariatric patients experienced a non-significant trend towards lower infection rates compared to controls matched by BMI (HR 1.3; 95% CI 0.8-20.3) [23]. It is suspected that in patients undergoing bariatric surgery prior to TJA, the risks for PJIs are reduced due to decreasing BMIs, but is offset by the increased risk for malnutrition. Improved patient stratification (e.g., malnutrition workup) may allow for better risk appraisal of these patients preoperatively.

Malnutrition (Modifiable)

Evidence Strength: Strong

The estimated prevalence of malnutrition in TJA patients ranges from 27 to 50% [24–26]. Malnutrition patients can be described using a variety of markers including serum albumin < 3.5 g/dL, total lymphocyte count < 1,500/mm^3, and/or transferrin < 200 mg/dL [27,28]. Multiple reviews have supported the claims that the degree of malnutrition correlates with an increased risk of impaired wound healing, persistent wound drainage, PJI and low success rates of the initial irrigation and debridement (I&D) [29–35]. In a small cohort study by Lavernia et al., it was reported that 4.54% of patients with an albumin < 3.5 g/dL developed a deep infection versus 2.06% in controls [36]. Many other studies have confirmed malnutrition to be a significant risk factor for prolonged hospitalization and postoperative complications, particularly SSIs and PJIs [33,37]. In a prospective study of 779 primary TJA patients, Kamath et al. found the incidence of preoperative albumin < 3.5 g/dL to be 15% [38]. In a separate, matched cohort study, malnutrition (albumin < 3.5 g/dL) was determined to be an independent risk factor for PJIs (adjusted OR 3.00, 95% CI 1.56 to 5.75) [39]. In a propensity-matched, retrospective, American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database analysis of 34,800 TKA patients with preoperative albumin levels, Fu et al. reported that preoperative hypoalbuminemia was a strong predictor for multiple complications (OR 1.78, 95% CI 1.20 to 2.64) [16]. A retrospective cohort-control study of 49,603 TJAs reported the prevalence of hypoalbuminemia to be 4%, placing patients at a significantly higher risk of SSIs (risk rate (RR) 2.0, 95% CI 1.5 to 2.8) [40].

In a retrospective cohort, Jaberi et al. confirmed that malnutritioned TJA patients were more likely to develop a deep infection and require further treatment with I&D [28]. Of these I&D patients, 35% continued to fail. Bohl et al. found that patients with hypoalbuminemia were three times more likely to have an indication of sepsis for revision arthroplasty (RR 3.8, 95% CI 3.4 to 4.3), and twice as likely to develop PJIs within 30 days of revision for aseptic indications (RR 2.1, 95% CI 1.2 to 3.5) [41]. A retrospective cohort study of 501 revision TJAs for PJIs noted the incidence of at least one laboratory parameter suggestive of malnutrition was 51% (OR 2.3, 95% CI 1.5 to 3.5) [32]. After multivariate analysis, Yi et al. found that malnutrition was a significant risk factor for chronic septic failures (OR 2.131, 95% CI 1.294 to 3.512) and acute PJIs complicating aseptic revision arthroplasty (OR 5.858, 95% CI 1.317 to 26.057). Severely malnutritioned patients are at

a significantly increased risk of PJIs/SSIs after primary TJA, and experience even more dramatic rates of failure and infection in revision procedures.

Malnutrition is therefore a relative contraindication for TJA. However, current guidelines recommending which patient populations to screen are currently absent. Severe malnutrition (serum albumin < 3 g/dL), however, should be an absolute contraindication.

Diabetes Mellitus (Modifiable)

Evidence Strength: Strong

Outcomes regarding PJIs in diabetic patients have been controversial. In a retrospective cohort study of 56,216 knees, the diagnosis of diabetes was reported to confer a 1.28 (HR; 95% CI 1.03 to 1.60) greater risk for PJIs, when compared to non-diabetic controls [42]. In a Chinese study of 1,133 TKAs by Lee et al., diabetes was reported to be associated with a 6-fold (OR 6.07; 95% CI 1.43-25.75) increased risk for PJI when compared with unmatched controls [43]. In a separate study based on Chinese patients, Wu et al. showed an adjusted risk for PJIs of 5.47 (95% CI: 1.77 to 16.97) over controls. Several metanalyses have also reported a significantly elevated rate of PJIs within the diabetic population [19,42,44–48].

Conversely, in a high-quality study utilizing the Mayo Clinic Total Joint Registry, diabetes was reported not to be a risk factor for PJIs (HR 1.23; 95% CI 0.87 to 1.74) when confounding variables were appropriately adjusted for age, gender, BMI, type of surgery (THA vs. TKA), American Society of Anethesiolgists (ASA) score and operative time [49]. A separate high-quality retrospective database study by Martinez-Huedo et al. also demonstrated no substantial increases in PJIs in diabetic patients undergoing THAs (0.46 vs. 0.44%) or TKAs (0.24 vs. 0.24%) [50]. Similar to the Mayo Clinic Joint Registry report, this study extensively matched patient cohorts by variables including: year of surgery, age, sex and all of the comorbidities listed in the modified Elixhauser Comorbidity Index. Together, they indicate that diabetes may not be the primary driver of postoperative PJIs. Instead, confounding variables such as diabetic end-organ damage (e.g., chronic kidney disease, vascular disease, etc.), may be the underlying cause for PJIs in this population.

Studies regarding the utility of perioperative glucose and preoperative hemoglobin A1c (HbA1c) monitoring have also been highly heterogeneous [49,51–56]. In the Mayo Clinic Joint Registry study, after adjusting only for age and gender, perioperative glucose (+/-1 day/week) and preoperative HbA1c monitoring were not found to correlate with postoperative PJIs [49]. In a study by Iorio et al., HbA1c was not significantly different between infected diabetic (HbA1c mean 6.2%; range 5.1 to 11.1%) and nondiabetic (HbA1c mean 6.92%; range 4.7 to 15.1%) TJA patients. Chrastil et al. showed a significant increase in PJIs when evaluating maximum perioperative glucose, particularly with a cutoff of ≥ 194 mg/dL (HR 1.44; 95% CI 1.10 to 1.89), but reported no increase in PJIs for patients with HbA1c > 7% (HR 0.86; 95% CI 0.68 to 1.1) [53]. However, when graphed, an evident inflection point for increased PJIs appeared when HbA1c levels rose above approximately 8 to 9%. Similarly, serum glucose demonstrated an overt increase in infection rates when glucose levels rose above ~200 mg/dL. A meta-analysis study by Shohat et al. only showed non-significant trends for increased SSIs when correlating PJIs with HbA1c levels in a pooled OR of 1.49 (95% CI 0.94 to 2.37). The study reported significant heterogeneities between studies ($I^2 = 81.32\%$; $p < 0.0001$).

Diagnosis of diabetes, preoperative hyperglycemia and elevated HbA1c are not likely direct risk factors for PJIs, but more likely to be indirect markers of more serious comorbid conditions (e.g., chronic kidney disease (CKD), peripheral vascular disease (PVD), etc.). Patients, with a sole diagnosis of well-controlled diabetes, do not confer a clinically significant risk for PJIs. However, further evaluation and optimization are necessary for patients with uncontrolled diabetes, end-organ damage or other clinically relevant comorbid conditions. Elevated perioperative glucose and HbA1c are equivocal in predicting PJIs, but should still be optimized in the perioperative period. However, severely uncontrolled diabetes is an absolute contraindication for TJA (e.g., serum glucose ≥ 200 mg/dL). For those with HbA1c ≥ 8 to 9% or glucose levels between 180 to 200 mg/dL, optimization may be a consideration in the preoperative period.

Chronic Kidney Disease (CKD) (Modifiable)

Evidence Strength: Strong

In a retrospective database study by Cavanaugh et al., patients undergoing primary TJA with CKD/end-stage renal disease (ESRD) were associated with a significantly increased risk for SSIs when compared to matched, non-CKD/ESRD controls (OR 1.59; 95% CI 1.14 to 2.21) [57]. When stratified by a patient's dependence on hemodialysis, patients requiring dialysis were at significantly increased risk for SSIs compared to non-dialysis, CKD/ESRD controls (OR 2.44; 95% CI 1.27 to 4.70). When compared to CKD/ESRD patients who underwent renal transplant surgery, dialysis patients also fared significantly worse (OR 2.92; 95% CI 1.93 to 4.42).

The risks of SSIs/PJIs in patients that do not require dialysis is uncertain. In two large separate database studies by Kildow et al. and Erkocak et al., CKD versus non-CKD did not show elevated risks for SSIs or PJIs. However, it should be noted that patient-matching was more extensive in Cavanaugh's study, and that it is difficult to assess the severity of CKD progression in the large database studies.

In a Medicare database study, patients were divided into five cohorts: (1) diabetes mellitus (DM) and THA, (2) DM, THA, CKD, (3) DM, THA, Hemodialysis (HD), (4) DM, THA, Renal Transplant (RT) and (5) age/gender-matched controls. At 90-days, the risk for PJIs increased with worsening comorbidity status: DM/THA OR 2.85 (95% CI 2.54 to 3.19), DM/THA/CKD OR 4.19 (95% CI 3.58 to 4.91) and DM/THA/HD OR 6.61 (95% CI 4.25 to 10.27). DM/THA/RT demonstrated no significant increases in PJI risks over that of control (OR 1.12; 95% CI 0.60 to 2.07), but by 2 years DM/THA/RT became significant with an OR of 1.45 (95% CI 1.04 to 2.04). Compared to previous studies, the risk of PJIs due to diabetes may be synergistic with CKD. This risk is similar to that reported by Cavaughn et al. (OR 2.03, 95% CI 1.53 to 2.7) [57].

In summary, patients with CKD are at increased risks for postoperative SSIs, but require stratification to adequately assess their risk. Current evidence suggests that patients with ESRD requiring hemodialysis fare worse than non-hemodialysis CKD and renal transplant patients. With the reduced risks for postoperative SSIs/PJIs, patients on hemodialysis should be evaluated for renal transplant prior to TJAs.

Clotting Disorders (Non-modifiable)

Evidence Strength: Moderate

Comparative studies examining the effects of clotting disorders and risks for PJIs/SSIs are limited, with most studies reporting only on the natural history or incidence. In a study by Cancienne et al., the risk of PJIs in two cohorts undergoing primary TKAs, hemophiliacs and patients with von Willebrand's disease were compared against those of matched controls without a bleeding disorder [58]. At 3 months, hemophiliacs suffered from a 1.5 greater odds (95% CI 1.2 to 2.0) for PJIs, and patients with von Willebrand's disease trended towards 1.4 greater odds (95% CI 0.9 to 2.1) for PJIs. PJI rates were marked by six

months for both groups (hemophilia OR 1.6 (95% CI 1.4 to 2.0); von Willebrand's disease OR 1.5 (95% CI 1.1 to 2.0)). Large cohort database studies demonstrate inconsistent findings regarding coagulopathies [18,59–61]. However, these studies have failed to sub-analyze the underlying pathologies (e.g., Vitamin K deficiency, von Willebrand's disease, etc.) responsible for abnormal clotting, therefor potentially confounding results.

Currently, the study by Cancienne et al. is the largest, comparative study directly assessing patients with blood clotting disorders. Patients afflicted by clotting disorders are more likely to suffer from PJIs due to their increased risks for hemoarthropathies. Management of these patients, particularly with regards to venous thromboembolism (VTE) prophylaxis, remains challenging. Patients with clotting disorders are relative contraindications to TJA.

Previous Infection of the Operative Joint (Non-modifiable)

Evidence Strength - Strong

In a retrospective cohort study by Pugely et al., patients undergoing elective primary TJAs with a history of previous wound infection were reported to be at a 5.0 greater odds (95% CI 2.3 to 10.9) for SSIs when compared to patients without a history of joint infections [62]. Similarly, in a study of patients afflicted by RA, history of joint infections also resulted in increased risks for postoperative PJIs (OR 5.4; 95% CI 1.87 to 16.14) [63]. Patients reporting previous infections of the joint should be evaluated for active infections with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Surgery should be delayed for those with markers of active infections.

Active Infection (Modifiable)

Evidence Strength - Strong

Systemic or local tissue infections have also been associated with hematogenous or direct seeding of the prostheses after TJA [64–70]. Active infections of an arthritic joint have also been proven to increase the rates of PJIs after TJA substantially [71,72]. A retrospective case-control study found that active *Staphylococcus* septicemia was associated with an increased risk of SSI OR 4.87 (95% CI 1.44 to 15.35) [73]. More interestingly, Radtke et al. reported that preoperative systemic extended-spectrum beta-lactamase bacterial infections within 15 months of THAs significantly increased the risks for PJIs (OR 20.13) [74]. Grammatico-Guillon et al. reported that patients with active ulcers preoperatively had significantly higher rates of SSIs following TJA versus those without ulcers (HR 2.55; 95% CI 1.94 to 3.35) [75]. The authors also showed that patients with urologic inflammatory diseases have also been noted to have increased risks for SSIs after TJAs. However, randomized control trials and metanalyses have indicated that patients with asymptomatic bacteriuria do not appear to be at increased risks for PJIs [76,77]. Moreover, PJI cultures were never the same as the urologic cultures. Larger database studies and retrospective chart reviews have demonstrated no associations between urinary tract infections and PJIs [59,60,78].

In summary, to prevent the catastrophic sequelae of PJIs, active infections of the joint, bloodstream or local tissue are an absolute contraindication to surgery and should be managed prior to performing a TJA.

Human Immunodeficiency Virus (HIV) (Modifiable)

Evidence Strength: Moderate

In a cohort study utilizing the National Inpatient Sample (NIS) database between 1998 and 2010, HIV(+) patients demonstrated a significant 2.78 odds (95% CI: 1.15 to 6.72) of developing SSIs [79]. A similar study by Schairer et al. also reported a 2.06 (95% CI: 1.31 to 3.26) greater odds for PJIs in HIV/Aquired Immune Deficency Syndrome (AIDS) patients, but did not differentiate between the two cohorts. The effects became more evident in the study by Tan et al., which demonstrated 4.44 greater odds (95% CI: 2.47 to 7.99) for PJIs in the AIDS patient population. More recent cohort studies, such as those by Capogna et al. and Lin et al., reported only non-significant trends towards increased infections (OR 6.6 (95% CI 0.64 to 61.0) and OR 3.8 (95% CI 0.06 to 76.75), respectively) in cohorts with HIV [80–82]. Arguably, these discrepancies may be the result of improved HIV antiretroviral therapies and protocols.

Hepatitis co-infection should be investigated and addressed in all patients with HIV. The estimated incidence of hepatitis C co-infection is reported to be 23.2 to 37.0%, and co-infection with hepatitis B is 10.1 to 24.0% [80,83]. In a matched-cohort Medicare database study by Kildow et al., patients were stratified by concomitant hepatitis infections: (1) HIV, (2) hepatitis B virus (HBV), (3) hepatitis C virus (HCV), (4) HIV with HBV or HCV and (5) matched HIV(-) controls [84]. When examining HIV (+) patients only, PJI infections at 90-days post-TKA/THA and 2-years post-THA were not significantly different from HIV(-) controls. Conversely, PJI risks in HIV(+) with HBV(+) or HCV(+) patients were elevated at 90-days post-TKA (OR 2.32; 95% CI 1.27 to 4.25), 2-years post-TKA (OR 2.17 1.48 to 3.18) and 2-years post-THA (OR 2.67 1.59 to 4.47) when compared to matched HIV(-) and HBV(-) and HCV(-) controls.

Similarly, in a meta-analysis of PJIs in HIV only versus HIV with hemophilia patients, hemophilia conferred a 5.28 greater odd (95% CI 2.24 to 11.98) for PJI [85]. A separate analysis was also carried out examining the effects of HIV with and without highly active antiretrovial therapy (HAART) for PJI [85]. Patients receiving HAART were found to have a significantly reduced risk (OR 0.12; 95% CI 0.03 to 0.44) for PJIs [57].

Current recommendations regarding TJAs in patients with HIV indicate all patients undergoing TJA should be initiated on HAART therapy immediately, regardless of CD4+ counts and viral load. Untreated HIV patients are absolutely contraindicated for TJAs. However, due to the logistical nature of clinical studies, no studies to date have been developed to adequately correlate, stratify or control for CD4+ counts and HIV viral loads in relation to PJI outcomes. It is recommended that patients on HAART therapy maintain a preoperative CD4+ count of at least ≥ 200 or greater.

MRSA Colonization (Modifiable)

Evidence Strength: Strong

Outcomes regarding methicillin-resistant *Staphylococcus aureus* (MRSA) colonization in TJA patients have primarily been studied in small sample sizes with highly variable outcomes. Kalmeijer et al. determined that high-level nasal carriage of *S. aureus* was a significant independent risk factor with a risk rate (RR) of 16.0 (95% CI 3.1 to 82.2) for developing an *S. aureus* SSI [86]. Subsequent studies have also demonstrated that THA patients colonized by MRSA have an elevated relative risk for SSIs of 4.46 (CI 95% 1.12 to 17.82; 5.26 vs. 1.17%) when compared to non-colonized cohorts [87]. Similarly, in TKA patients, the RR for SSIs was 5.61 (95% CI 1.81 to 17.38; 7.32 vs. 1.3%). A retrospective analysis of patients with PJI reported *S. aureus* colonization to have a 3.97 greater odds (95% CI 1.49 to 10.54) for PJI compared to control groups [88]. Furthermore, *S. aureus* colonization has been found to have an additive effect with active tobacco use, revision surgery, and/or BMI ≥ 30 kg/m^2, increasing the risk 3 to 12 times that of controls [89]. A number of prospective studies and systematic reviews in both the orthopaedic and general surgery literature

have reported rapid screening and decolonization of *S. aureus* nasal carriers on admission to be effective [90,91].

S. aureus screening and treatment are quick, inexpensive and simple and should be performed on all patients prior to surgery. A small number of patients do not respond to treatment and remain chronic carriers. Although their risk remains elevated for PJIs, continued *S. aureus* colonization is a relative contraindication to elective primary TJA, but may be managed with intraoperative, local vancomycin. However, the use of vancomycin must be balanced against the risk for acute kidney injury [92].

Bacterial Skin Colonization Other Than MRSA (Modifiable)

Evidence Strength: Strong

Preoperative chlorhexidine-based skin preparation has been proposed as a method of reducing SSIs. In a randomized control trial by Kapadia et al., use of chlorhexidine-impregnated clothes the night before or the morning of admission reduced the 1-year PJI rate by 2.5% (2.9 vs. 0.4%) when compared to the previous standard of care (OR 8.15; 95% CI 1.01 to 65.6) [93]. Similar results have been observed in a previous retrospective cohort study (in the same institution) [94,95], as well as in the general surgery patient population [96].

Hepatic Disease

Evidence Strength: Strong

Hepatitis (Modifiable)

A retrospective study by Kuo et al. looking at 3,435 TKA patients in the Taiwanese Longitudinal Health Insurance Database reported that males with HBV had a 4-fold, (OR; 4.32; 95% CI 1.85 to 10.09) increased risk of PJIs compared to those without HBV [97]. The PJI risk was highest 6 months to 1 year following TKA (HR 18.7; 95% CI 1.90 to 184) and decreased after the first year (HR 4.8; 95% CI 1.57 to 14.7). The authors reported no differences in PJI incidences between patients without HBV in the first month. The presence or absence of cirrhosis and HCV infection did not further influence PJI risks in these patients. Interestingly, HBV did not appear to significantly increase the risk of PJIs for females.

In a retrospective, matched control study of 77 HCV(+) TJAs, there were no differences in PJI incidences in HCV(+) versus HCV(-) patients [98]. However, of the two infections in the HCV(+) group, both were deep infections that required reoperation. Meanwhile, both infections in the control group only reported superficial infections that were treated with IV antibiotics. When the HCV cohort was further stratified by disease progression, the incidence of PJIs was noted to be markedly higher in patients whose disease progressed to fibrosis (21 vs. 0%). Kildow et al. reviewed 22,663 TJA patients using the PearlDiver Medicare database and found increased TJA PJI risks for HCV(+) patients at 90-days (OR 1.96; 95% CI 1.53 to 2.50) and 2 years (OR 1.93, 95% CI 1.66 to 2.25), as well as in HBV(+) patients at 2 years (OR 1.66; 1.06 to 2.59) [99]. Although not directly compared to one another, concomitant HIV infection appears to increase infection rates further. With new HCV treatments, it will be important to observe the effects of HCV resolution and PJI outcomes.

Liver Cirrhosis (Modifiable)

To better delineate the effects of cirrhosis versus hepatitis, Jian et al. performed a matched control cohort study using 880,786 TJA patients from the NIS database [82]. When compared to controls, HBV(+) patients without cirrhosis were found to be at no increased risk for PJIs (1.22 (HR; 95% CI 0.77 to 1.95), while HCV(+) patients without cirrhosis were at a 2-fold greater risk for PJI (HR 2.33; 95% CI 1.97 to 2.76), and patients with cirrhosis were at 2.42 greater odds for PJIs (95% CI 1.87 to 3.12). In a large Danish database study by Deleuran et al., deep infection at one year was higher in cirrhotic patients than matched controls (OR 1.65; 95% CI 0.61 to 3.56; 3.1 vs. 1.4%) [100].

Other small, retrospective studies regarding liver cirrhosis demonstrated mixed results. Seol et al. retrospectively compared 71 cirrhotic patients undergoing elective TJA against non-cirrhotic controls [101]. Only a non-significant trend towards increased PJIs (13.5 vs. 5.6%) and SSIs (17.6 vs. 2.8%) was found. It was also noted that most patients who experienced surgical complications were more likely to have chronic comorbidities (e.g., CKD, diabetes and hypertension). Other older studies have described increased rates of wound complications after elective TJAs in patients with asymptomatic liver disease and advanced cirrhosis [102,103]. Similarly, a small study by Cohen et al. has suggested that certain subgroups of cirrhotic patients, specifically Child-Pugh A and B, can safely undergo elective TJA with no increased risk of adverse events [104].

Transplant (Non-modifiable)

Regarding patients receiving a liver transplant, the relative risk of PJIs remains a debated topic, with many studies being only case series. Two case series reported an overall PJI rate of 3.2 to 3.6% [105,106]. A cohort study by Ledford and colleagues reported that organ transplants substantially increased the risks of SSIs or PJIs (3.2%), but there were no differences between groups [106]. One study, which utilized the NIS database, compared the outcomes of 4,493 TJA patients with a history of organ transplantion and revealed that liver transplantion had the greatest increased risks of wound infections and SSIs (OR 3.90, 95% CI: 1.4 to 3.9) compared to kidney, heart, lung and pancreas transplantions [57].

HBV, HCV, cirrhosis and hepatic transplant are relative contraindications to surgery. However, both HCV and cirrhosis present as potentially modifiable risk factors with the advent of HCV immunotherapies and transplant surgeries, respectively. Preliminary evidence points towards HCV treatment prior to TJA. Additionally, the degree of liver cirrhosis and potential risks can be assessed based on the efficacy of serum clotting factors. Due to the lack of conclusive evidence, no strong recommendations can be given at this time for or against HCV immunotherapy, cirrhosis optimization or hepatic transplant prior to TJA. Hepatic panels and coagulation panels should be assessed in patients with end-stage liver disease and surgery should delayed if any bleeding deficiencies are noted.

Chronic Anticoagulation (Non-modifiable)

Evidence Strength: Low

In a matched case-control study by Simpson et al., chronic preoperative warfarin therapy in TKA patients led to: substantially increased hematoma formations within 48 hours (26.8 vs. 7.3%), superficial infections (16.8 vs. 3.3%), deep infections (6.0 vs. 0%) and returns to the operating room (OR) for washout (4.7 vs. 0.7%) [107]. Subset analysis of patients who required heparin-bridging demonstrated markedly higher, deep infection rates when compared to patients who continued warfarin. A similar matched case-control study of THA patients also reported increased rates of deep infections (9 vs. 2.2%) and superficial infections (13.5 vs. 2.2%) [108].

Due to the absence of strong, conclusive evidence or management guidelines, it is recommended for patients on warfarin therapy to be evaluated for other risk factors and optimized appropriately to mitigate the risks of PJI. Bridging of patients on warfarin should be avoided and only performed if absolutely necessary. Future studies

are needed to examine the relationship of International Normalized Ratio (INR), as well as modern-day heparin analogues (e.g., factor Xa inhibitors), with infection.

Alcohol Consumption (Modifiable)

Evidence Strength: Strong

A recent meta-analysis found that alcohol use had a two-fold risk of PJI following TJA (OR 1.88, 95% CI 1.32 to 2.68) [44]. Wu et al. reported similar outcomes in a retrospective study of Chinese patients undergoing TJA (OR2.95; 95% CI, 1.06 to 8.23) [45]. A large, retrospective, matched-control study of 880,786 Statewide Inpatient Database patients illustrated that alcohol use significantly increased the PJI risk after TJA (HR 1.64, 95% CI 1.38 to 1.95) and represented an additive risk factor when present concomitant to cirrhosis [82]. Grammatico-Guillon et al. retrospectively analyzed 32,678 patients in the French Regional Hospital Discharge database and found that alcohol abuse was correlated with a significant increase in SSI risk (HR 2.47, 95% CI 1.67 to 3.63) [75]. The major impact of alcohol abuse on PJI rates was demonstrated by Radtke et al. [74]. After retrospectively reviewing 566 THAs, alcohol abuse was found to increase the odds of PJI by 5.59 (95% CI 95% CI 1.14 to 27.33) within 18 months of surgery. Alcohol consumption has therefore been clearly shown to increase the risk of PJIs for patients undergoing TJAs [18,59–61,109,110]. While there is no defined period of required alcohol cessation prior to TJA, at least four weeks of abstinence has been suggested to reverse physiologic abnormalities associated with excessive alcohol use that predispose patients to increased risk of postoperative morbidity [111].

Alcohol consumption must be assessed on a case-by-case basis. Excessive alcohol consumption is a modifiable risk factor that is a relative contraindication for elective TJA until patients remain abstinent for a minimum of four weeks. However, patients who remain functional in good socioeconomic standing may not require surgical delay.

Smoking (Modifiable)

Evidence Strength: Strong

A recent review reported that 18% of the U.S. population are smokers, placing them at an RR of deep infection after TJA 3.5 times higher than the average population [112]. Tobacco use is growing in the obese population and carries eight times the risk of infection compared to non-obese, non-smokers [88]. In a study by Maoz et al., tobacco use, *S. aureus* colonization and BMI ≥ 30 kg/m^2 were additive in their risks for PJIs (OR 12.76; 95% CI 2.47 to 66.16) [89]. A 2:1 matched-cohort study reported significantly higher surgical complication rates (3.6%) in smokers compared to nonsmokers (0%). Moreover, the majority of revision TJAs performed in the smoking cohort were secondary to infection [113]. In their ACS NSQIP database study, Duchman et al. described a significant increase in the risk of wound complications after TJA in tobacco users (OR 1.47, 95% CI 1.21 to 1.78) [114]. In a comparable large database study, Kremers et al. conveyed similar outcomes with an increased risk of SSI in smokers (HR 1.7, 95% CI 1.1 to 2.6) [115]. Although Singh et al. did not find a significant difference in the rate of SSI in smokers, the authors reported a substantial risk for PJIs when compared to a matched nonsmokers control group (HR 2.28, 95% CI 0.99 to 5.27) [116]. Sahota et al. performed a propensity, score-matched analysis of 12,588 TJA patients in the ACS NSQIP database to assess the effects of smoking on 30-day postoperative complications. The overall 30-day surgical complication rate was higher in current smokers at 2.5% compared to 1.4% in nonsmokers (OR 1.84, 95% CI 1.21 to 2.80). Smokers also exhibited a markedly higher rate of 30-day deep SSIs (1.1%) in a combined THA/TKA cohort. Upon subgroup analysis, active smokers experienced substantially higher incidences of 30-day deep SSIs after THAs (1.3%) and 30-day superficial SSIs following TKAs (1.8%) [117]. A prospective, hospital-registry-based cohort study by Gonzalez et al. found that current smokers had higher one-year postoperative PJI rates than former smokers, both of which were significantly higher than never-smokers (HR 1.8, 95% CI 1.04 to 3.2). Beyond the first year of surgery, the risks of PJIs decreased slightly but remained significantly elevated compared to a history of no smoking (HR 1.12, 95% CI 0.64 to 2.04) [118]. A meta-analysis of six randomized trials demonstrated that smoking cessation had a relative risk reduction of 41% of total postoperative complications. In the same study, the authors pooled data from 15 observational studies and found that patients who discontinued smoking prior to surgery had decreased wound healing complications (RR 0.73, 95% CI 0.61 to 0.87) [119]. On the other hand, Azodi et al. reported that patients partaking in smoking a higher number of packs per year resulted in a significant increased risk of postoperative complications [120]. Moreover, after adjusting the multivariate logistic analysis, the heaviest tobacco smoking group had a 121% increased risk of systemic complications (OR, 2.21; 95% CI 1.28 to 3.82). Smoking represents an independent, modifiable risk factor that significantly compounds the risks of SSIs/PJIs when present alongside other comorbidities. Therefore, active smoking, especially heavy tobacco use, represents a relative contraindication to TJA until enrolled in a smoking cessation program for at least four weeks.

Intravenous Drug Abuse (Modifiable)

Intravenous drug abusers (IVDA) can often present with HIV, creating a myriad of risks that are problematic to treat. Previous retrospective studies have described a four-fold increase in septic arthritis of native joints in IVDA versus non-IVDA patients [121,122]. A retrospective study by Lehman et al. reported higher rates of PJIs in IVDA and/or HIV(+) patients [123]. IVDA also carried almost twice as high PJI incidences (25%) compared to HIV(+) only patients(14%). When IVDA and HIV were both present, the rates of PJIs increased to 40%. More recent studies confirmed that IVDA was a significant risk factor for THAs and resulted in higher odds of PJIs in orthopaedic surgery [109,124]. The risks of PJIs continue well past the primary TJA, and substantially impacts ensuing revision procedures. Su et al. reported an estimated 25% survival, free of reinfection rates, for two years in IVDA patients compared to 96% in control revision THA patients [125]. Pitta et al. conducted a prospective cohort study of 405 failed primary TKAs [126]. Their study demonstrated that IVDA was a significant risk factor for TKA failure and correlated with a five-fold increase in risk for revision surgery. Two retrospective reviews of IVDA within 1 year of THA and TKA described failure rates as high as 50%, complicated revision procedures and a 17% amputation rate [127,128]. The unacceptable PJI rates, leading to complex salvage procedures and high failure rates after primary and revision surgeries, make TJA in active IVDAs futile and an absolute contraindication. Patients should be referred to appropriate drug counseling programs and be offered surgery only after remaining abstinent from drug use for a minimum of one year.

Osteonecrosis (Non-modifiable)

Evidence Strength: Moderate

Evidence regarding osteonecrosis and its relation to SSIs/PJIs is highly conflicting. Currently, the three identified studies in this systematic review were all derived from the Kaiser Permanente Total Joint Replacement Registry (TJRR). In two studies by Namba et al.,

similar methods were applied to evaluate the effects of osteonecrosis on SSIs/PJIs; one focused on THAs while the other focused on TKAs [42,129]. Both studies demonstrated an increased risk for SSIs/PJIs in TJA candidates with osteonecrosis. However, a third study by Singh et al. [130], which contained many overlapping authors from the Namba et al. studies and utilized the TJRR, extended the original 8-year database to 11 years, and found no increases in SSIs/PJIs in THA candidates with osteonecrosis. Due to the conflicting evidence and high potential for study bias, osteonecrosis of the hip is not a strong risk factor for SSIs/PJIs in TJA candidates.

Age (Non-modifiable)

Evidence Strength: Moderate

There is inconsistent evidence on whether age contributes to increased risks of PJIs. The meta-analysis by Chen and colleagues showed no associations between age and risk of infection [46]. In a pooled analysis of eight studies, age (as a continuous exposure) was not associated with the risks of PJI [19]. However, findings from two studies suggested that patients 75 years old and above had an increased risk of SSIs following primary THAs [131,132].

Gender (Non-modifiable)

Evidence Strength: Moderate

The effects of gender on the risks of PJIs have been mostly inconsistent. While some studies suggest males are at an increased risk of developing PJIs following joint arthroplasty, others suggest the contrary. In a pooled analysis of eight studies, Chen et al. demonstrated that males had a higher risk of infection after TKA than females [46]. Recent pooled multivariate analysis of 28 studies confirms the emerging evidence [19].

Race (Non-modifiable)

Evidence Strength: Strong

Pooled analysis shows that black and Hispanic populations have increased risks of developing PJIs/SSIs, when compared to white populations [42,61,133].

Location (Non-modifiable)

Evidence Strength: Limited

One study reported an increased risk of infections for patients residing in rural locations as opposed to urban locations in China [45]. However, this may be the result of a country's care system as opposed to geographic location.

Hip vs. Knee Arthroplasty (Non-modifiable)

Evidence Strength: Strong

Compared to THAs, TKAs were consistently associated with increased risk of PJIs/SSIs [73,134].

Underweight (Modifiable)

Evidence Strength: Strong

Three studies compared underweight (BMI < 18.5 kg/m^2) vs. normal vs. overweight BMI categories and found no associations with PJIs [13,14,129].

Hypertension (Modifiable)

Evidence Strength: Strong

Pooled analysis of four large database studies with matched controls showed no significant evidence of associations between hypertension and the risks of PJIs/SSIs [18,59,60,135].

Socioeconomic Status (Non-modifiable)

Evidence Strength: Strong

Consistent evidence showed that a low income was associated with increased risks of PJIs/SSIs [136–138].

Electrolytes (Modifiable)

Evidence Strength: Strong

There was no significant evidence of associations between electrolyte imbalances and risks of PJIs/SSIs [18,62].

Depression (Modifiable)

Evidence Strength: Strong

Evidence suggested histories of depression and psychosis to be associated with increased risks of PJIs following TJA [18,59,60].

Steroids (Modifiable)

Evidence Strength: Moderate

A previous meta-analysis of four studies suggested a history of steroid therapy to be associated with increased risks of PJIs following TKAs [46]. In a pooled analysis of five studies, Zhu et al. also demonstrated steroid therapy to be associated with increased risks of PJIs following TJA [48]. In the most recent pooled analysis of 10 studies, the findings were consistent with previous evidence [19].

Cardiovascular Disease (CVD) (Modifiable)

Evidence Strength: Strong

A pooled analysis of seven studies reporting inconsistent findings showed a history of CVD to be associated with increased risks of PJIs/SSIs following TJAs [59,60,78,139–143]. In a pooled analysis of studies that evaluated congestive heart failure (CHF) and cardiac arrhythmias as risk factors, significant associations were demonstrated [5,18,59,60,133].

Peripheral Vascular Disease (PVD) (Modifiable)

Evidence Strength: Strong

A pooled analysis of six studies should a history of PVD is associated with increased risks of PJIs/SSIs [5,18,59,60,82,144].

Lung Disease (Modifiable)

Evidence Strength: Strong

The presence of chronic pulmonary diseases remains equivocal. While pooled analysis of four studies evaluating the associations of chronic pulmonary disease with risk of PJIs showed no evidence of an association [5,59–61], two studies reported consistent associa-

tions. With regards to chronic obstructive pulmonary disease, specifically, an increased risk for PJIs/SSIs was noted in a pooled analysis of four studies [3,73,133,135].

Rheumatoid Arthritis (RA) (Modifiable)

Evidence Strength: Moderate

A pooled analysis of seven studies showed RA to be associated with increased risks of PJIs following TKAs [46]. In another pooled analysis of seven studies, Zhu et al. demonstrated RA to be associated with increased risks of PJI [48]. Findings of a recent pooled analysis of 13 studies confirms the accumulating evidence [19] .

Malignancy (Non-modifiable)

Evidence Strength: Strong

A history of cancer or malignancy was associated with increased risks of PJIs/SSIs following arthroplasty in a pooled analysis of seven studies [18,59–61,73,145,146]. However, evidence on the associations between metastatic tumors and risks of PJIs/SSIs was limited and inconsistent [5,18,59,60].

Previous Joint Surgery (Non-modifiable)

In a pooled analysis of five studies, a history of previous joint surgery (vs. no previous joint surgery) was associated with a threefold increased risk of PJIs [19]. When compared to primary arthroplasties, revision arthroplasties were associated with increased risks of PJIs in a pooled analysis of five studies [19]. Two studies reported a history of previous joint infections to be associated with increased risks of PJIs, but these findings were based on univariate analysis [3,63].

Frailty (Modifiable)

Evidence Strength: Moderate

A single, high-quality study reported increased risks of PJIs comparing frail patients with non-frail patients [147].

Anemia (Modifiable)

Evidence Strength: Strong

Consistent evidence showed that preoperative anemia was associated with increased risks of PJIs/SSIs following TJAs [5,59,60,148].

ASA (Non-modifiable)

Evidence Strength: Strong

An ASA grade of > 2 was associated with increased risks of PJIs/SSIs; this was consistent across all studies [42,89,129,131,133,134].

Charlson Comorbidity Index (Modifiable)

Evidence Strength: Strong

Though the exposures were not comparable, and therefore could not be pooled, there was consistent evidence showing a higher Charlson Comorbidity Index to be associated with an increased risk of PJIs/SSIs [136,137,149].

Osteoarthritis (Non-modifiable)

Evidence Strength: Strong

Pooled evidence from seven studies showed no significant associations of osteoarthritis with the risks of PJIs following joint arthroplasties [42,109,129,130,150,151].

Post-Traumatic Arthritis (Non-modifiable)

Evidence Strength: Strong

Pooled analysis of three studies showed no evidence of associations between post-traumatic arthritis and risks of PJIs/SSIs [42,129,152].

Dental Procedures (Non-modifiable)

Evidence Strength: Limited

In two studies that evaluated the associations of dental procedures with risks of PJIs, there was no evidence of any significant associations [45,145].

Neurologic (Modifiable)

Evidence Strength: Strong

A history of neurologic disease such as hemiplegia/paraplegia was associated with increased risks of PJIs/SSIs in a pooled analysis of four studies with inconsistence findings [59–61]. The results were the same for dementia and PJIs/SSIs [59,60,73].

Hypercholesterolemia (Modifiable)

Evidence Strength: Strong

None of the studies, which evaluated the associations of hypercholesterolemia and peptic ulcer disease with the risks of PJIs, showed any evidence of associations [18,59,60].

Valvular Disease (Non-modifiable)

Evidence Strength: Strong

Evidence regarding the associations between valvular diseases and risks of PJIs/SSIs was limited and inconsistent [18,59–61]. In the pooled analysis, there was no significant evidence of PJIs/SSIs being associated with a history of pulmonary circulatory disorders [5,59–61], a history of hypothyroidism [18,59,60,153], or a history of drug abuse [18,59,60].

Transfusion (Non-modifiable)

Evidence Strength: Strong

Patients who receive allogenic blood transfusions are at increased risks of SSIs/PJIs [5,134,154–156]; however, the evidence is limited for autogenic blood transfusions [5]. Prophylaxis with warfarin or low molecular weight heparin for venous thromboembolism was associated with increased risks of PJIs [157,158].

Methods and Materials: Manuscripts pertaining to host-related risk factors for PJIs were searched using PubMed, ScienceDirect, and Web of Science, with a date restriction of January 1, 2013 to February 23, 2018. The following search queries and their results are listed in the following chart:

Database	Search Term/Filter	Results
PubMed	("arthroplasty, replacement, hip"[MeSH Major Topic] OR "arthroplasty, replacement, knee"[MeSH Major Topic]) OR ("knee"[TITLE] OR "hip"[TITLE]) AND ("arthroplasty"[TITLE] OR "replacement"[TITLE]) AND ("infection"[MeSH Major Topic] OR "deep infection"[TITLE] OR "PJI"[TITLE] OR "Prosthetic Joint Infection"[TITLE] OR "Periprosthetic Joint Infection"[TITLE] OR "Surgical Site Infection"[TITLE] OR "SSI"[TITLE]) NOT ("autobiography"[Publication Type] OR "comment"[Publication Type] OR "congresses"[Publication Type] OR "dictionary"[Publication Type] OR "editorial"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "periodical index"[Publication Type] OR "personal narratives"[Publication Type] OR "technical report"[Publication Type] OR "webcasts"[Publication Type]) AND "last 5 years"[PDat] AND English[lang]	510
ScienceDirect	pub-date > 2012 and TITLE-ABSTR-KEY(((("hip arthroplasty" OR "hip replacement") OR ("knee arthroplasty" OR "knee replacement")) AND infection)	956
Web of Science	((TI=(("hip arthroplasty" OR "hip replacement" OR "knee replacement" OR "knee arthroplasty") AND (infection OR PJI OR SSI)))) AND LANGUAGE:(English) AND DOCUMENT TYPES: (Article OR Abstract of Published Item OR Data Paper OR Database Review OR Early Access OR Review)	246
	Total	1712

These results were subsequently imported into Mendeley Reference Management Software (Elsevier, Amsterdam, Netherlands) and 347 duplicates were removed. These abstracts were then imported into the Rayyan (Qatar Computing Research Institute, Doha, Qatar) for subsequent screening of titles and abstracts by authors J.E.F. and Z.C. Of the 1,365 abstracts collected, 1,126 were excluded due to incorrect study topic, foreign language, or low study quality (case reports and case series without comparative groups). Of the remaining abstracts, 239 remained for full-text article review with study quality assessment using the American Academy of Orthropaedic Surgeons (AAOS) Clinical Practice Guideline and Systematic Review Methodology guidelines [159]. The Relative Risk, Odds Ratios, and Hazard Ratios, as well as incidences and statistical significances, were used to assess outcomes of prosthetic joint-related infections.

A separate systematic review was performed by S.K. Data sources included Medline, Embase, Web of Science, Cochrane Library and reference lists of relevant studies from inception to February 15, 2018. Studies of interest were longitudinal studies (observational studies and randomized controlled trials (RCTs)) that have evaluated the associations of patient-related factors and the risk of SSIs and/or PJIs in patients undergoing orthopaedic procedures. Of 7,177 potentially relevant citations, 69 studies were finally included in this review. No RCTs relevant to the review topic were identified.

What modifiable and non-modifiable host factors contribute to an increased risk of SSI/PJI?

Modifiable host risk factors for PJI/SSI in TJA:

- Active Infection
- Alcoholism
- Cardiovascular Disease
  - Congestive Heart Failure
  - Cardiac Arrhythmia
- Chronic Kidney Disease
- Chronic Obstructive Pulmonary Disease
- Clotting Disorders
- Depression
- Diabetes Mellitus
  - HbA1c
  - Serum Glucose
- Drug Abuse
- End-stage Renal Disease
- Frailty
- HIV/AIDS
- Immunosuppression
- Intra-articular Steroid/Viscosupplement Injection
- Kidney Disease
- Malnutrition
- MRSA Colonization
- Obesity
- Peripheral Vascular Disease
- Psychosis
- Renal Disease
- Rheumatoid Arthritis
- Skin Colonization
  - MRSA/MSSA
- Smoking
- Untreated HCV

Non-modifiable host risk factors for PJI/SSI in TJA:

- Age
- ASA >2
- Bariatric Surgery
- Chronic Anticoagulation
- Gender
- Hemiplegia/Paraplegia
- HBV
- Osteonecrosis
- Previous Joint Surgery
- Previous Joint Infection
- Previous Infection
- Transplant

In addition to identifying pertinent risk factors for PJIs, what is the acceptable total risk for patients undergoing elective, primary

TABLE 1. Definitions

	Modifiable Risk Factor	Non-modifiable Risk Factor
Absolute Contraindication	**Absolute modifiable risk factor**: A risk factor that is associated with a preventable complication and delays surgery until it is appropriately evaluated and optimized.	**Absolute non-modifiable risk factor:** A risk factor that cannot be optimized and precludes the patient from receiving surgery. Alternative therapies for joint pain should be pursued.
Relative Contraindication	**Relative modifiable risk factor:** A risk factor that is modifiable but does not require surgical delay if no other risk factors are present. However, when the patient's risk for postoperative complications crosses the threshold of acceptability, this risk should be optimized.	**Relative non-modifiable risk factor:** A risk factor that is non-modifiable and does not require surgical delay. For patients with additional risk factors which cross the threshold of acceptability, other modifiable risk factors should be optimized prior to surgery.

TJAs? The Readmission Risk Assessment Tool (RRAT) was specifically developed to reduce the incidence of preventable hospital readmissions in patients undergoing elective TJA [160]. The RRAT includes eight distinct risk factors and uses a weighted score to quantify a patient's risk of readmission (e.g., MRSA colonization – 3 points, Smoking – 1 point, BMI ≥ 40 – 3 points, etc.). With nearly 45% of readmissions being due to SSIs, the RRAT is a powerful tool to identify and optimize patients at risk for PJIs. Despite the development of these powerful tools, a discussion regarding an ethically and financially acceptable risk cutoff for PJI is still required.

When does the accumulated relative risk of infection due to comorbidity burden (modifiable, non-modifiable or a combination) become unacceptable to proceed with TJA?

Examples:

- **Modifiable risk factors that are absolute contraindications (Absolute MRF):** Untreated HIV, serum glucose ≥ 200, active sepsis, active joint infection, intra-articular injections within three months, active intravenous drug use, super obesity (BMI ≥ 50 kg/m^2)
- **Modifiable risk factors that are relative contraindications (Relative MRF):** Obesity, elevated HbA1c, smoking, catastrophizers, high fall-risk patients, non-metastatic cancer, malnutrition, hepatitis C
- **Non-Modifiable risk factors that are absolute contraindications (Absolute Non-MRF):** Pulmonary hypertension
- **Non-modifiable risk factors that are relative contraindications (Relative Non-MRF):** Gender, age, hemiparesis, metastatic cancer, blood clotting disorders, hemophilia, von Willebrand's, previous infection of the operative joint, liver transplant, kidney transplant, hepatitis B

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QUESTION 2: Is the diagnosis of post-traumatic arthritis associated with increased risks of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) after joint arthroplasty?

RECOMMENDATION: Yes. Total joint arthroplasty (TJA) for patients with post-traumatic arthritis of the hip or knee carries higher risks of developing SSIs/PJIs. The incidence is markedly higher in patients with previous surgeries and retained implants.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 97%, Disagree: 1%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

Symptomatic arthritis of the hip, knee and ankle has been reported to be secondary to traumatic causes 12% of the time [1]. There have been few high-quality studies assessing the impacts of the preoperative diagnoses on the risks for SSIs and PJIs. However, numerous

studies have evaluated clinical and radiographic outcomes following TJAs for post-traumatic arthritis, but often lack a comparison group [1–14]. Moreover, studies have shown total knee arthroplasty (TKA) with retained hardware from a tibial plateau fracture is associated with a higher incidence of PJI compared to TKA for patients without retained hardware [15].

Bala et al. evaluated surgical complications among 3,509 patients undergoing TKA for post-traumatic arthritis in comparison to 257,611 controls from the Medicare database with at least two years of follow-up [1]. They found that post-traumatic arthritis patients were at a 4.93% risk of deep infection, compared to a 2.93% risk among the primary osteoarthritis group, for a significant odds ratio of 1.72 (95% confidence interval (CI) 1.47 to 2.01). Pedersen et al. used the National Danish Registry to evaluate risk for revision due to infection among 9,380 patients undergoing total hip arthroplasty (THA) due to arthritis following proximal femoral fractures compared to 63,318 control patients undergoing THA for primary osteoarthritis [16]. Post-traumatic THA patients experienced a 0.94% rate of deep infections, compared with 0.70% for primary osteoarthritis patients, for a non-significant difference in adjusted relative risk of 1.46 (95% CI 0.99 to 2.17). Similar results were observed in the Danish Knee Arthroplasty Registry that noted revisions were more frequent in post-traumatic arthritis knee patients [17]. Database studies have also been used to identify risk factors for SSIs/PJIs, which have shown higher infection rates in patients diagnosed with post-traumatic arthritis [18,19].

Saleh et al. performed a systematic review of TKAs for the treatment of post-traumatic arthritis that included 16 prospective and retrospective studies [10]. Primary outcomes focused on clinical function scores. Rates among the population that reported infection as a complication totaled 20.9% for superficial infections (62/296 total patients) and 16.5% for deep infections (67/405 total patients). No comparison groups were available for analysis among these studies. These proportions are higher than most published rates of PJIs for TKAs performed due to primary osteoarthritis. Similarly, a systemic review assessed the outcomes of THAs following acetabular fracture and noted that the risk of infections in THAs following acetabular fractures was higher than that for conventional hip arthroplasties, especially in patients with multiple prior surgeries and retained hardware from previous acetabular reconstruction [20].

Other studies provided proportions of PJIs as a secondary outcome among post-traumatic patients and primary osteoarthritis patients. Ge et al. performed a retrospective review of 27 patients who underwent TKAs following periarticular fracture compared to 45 patients who had a history of soft tissue injury about the knee without fracture [3]. Small numbers of PJIs were reported with two reported superficial infections in each group (7.4% vs. 2.3%) and four deep infections in the fracture group (15%) compared to zero in the soft tissue group. Lunebourg et al. reported on functional outcomes following TKAs. They compared 33 patients with a history of periarticular fractures with 407 primary osteoarthritis controls [6]. No superficial infections were reported in the post-traumatic group compared to one in the primary osteoarthritis group (0.02%), while two deep infections were reported in the post-traumatic group (6.1%) compared to zero in the primary osteoarthritis group. Scott et al. evaluated clinical outcomes of TKAs following tibial plateau fractures among 31 patients compared to a matched cohort of 93 primary osteoarthritis patients [12]. They reported four superficial infections in the post-traumatic group (12.8%) compared to one in the primary osteoarthritis group (1%). They reported one deep infection in each group (3.2% vs. 1%). Morison et al. performed a retrospective case-control study of patients who underwent THAs after acetabular fracture vs. a matched cohort of patients who had received THAs for primary osteoarthritis or avascular necrosis [21]. The authors observed that patients with a previous acetabular fracture had a higher likelihood of developing infections.

Further studies only reported infection rates for the post-traumatic patients without a comparison group. Proportion of patients experiencing infection in these studies ranged from 3.2 to 26.7% for superficial, and 3.2 to 20% for deep [2,4,5,7–9,11,13,14,22]. Only one study evaluated the risks of PJIs following THAs. All other included studies focused on PJIs following TKAs as a primary or secondary outcome. We conclude that a rate of PJIs following TJA for post-traumatic arthritis is likely higher than TJAs for primary osteoarthritis. However, few studies are evaluating this topic as a primary outcome, and the majority of these have limited number of infection events available for analysis.

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QUESTION 3: What nutritional markers are the most sensitive and specific for surgical site infections and periprosthetic infections (SSIs/PJIs)? Does improvement in nutritional status reduce the risk of SSI/PJI?

RECOMMENDATION: Serum albumin < 3.5 g/dL has been demonstrated to be an independent risk factor for SSIs/PJIs following total joint arthroplasty in multiple, large-scale studies. However, other nutritional markers are poorly studied. Currently, there is insufficient evidence to prove that correction of preoperative nutritional markers reduces the risks of subsequent SSIs/PJIs. Despite the absence of such evidence, we recognize the importance of an optimized nutritional status before total joint arthroplasty (TJA) to reduce the risks of SSIs/PJIs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

It is well established that malnutrition is associated with an increased risk of a number of adverse outcomes following TJA, including wound healing problems, longer hospital stays and PJIs [1–3]. The prevalence of malnutrition in patients undergoing orthopaedic procedures has been reported to be as high as 50% [4]. However, it is unclear which nutritional markers are most sensitive and specific for SSIs and PJIs. Serologic values and anthropometric measures have been utilized to determine nutritional status.

Serologic markers commonly used as markers of malnutrition include serum albumin concentration < 3.5 g/dL, serum total lymphocyte count (TLC) of <1500 cells/m^3 and serum transferrin < 200 mg/dL. Other serum markers, including serum prealbumin, have been discussed in nutritional literature but levels for malnutrition have been poorly defined in the orthopaedic literature.

Gherini et al. evaluated preoperative serum albumin and transferrin levels in patients undergoing primary total hip arthroplasty (THA) and found that delayed wound healing was associated with a lower preoperative serum transferrin (226 mg/dl in complicated cases vs. 262 mg/dl in those that did not have any complications) [5]. Alfargieny et al. found that serum albumin, but not serum TLC, was an independent predictor of SSIs following primary THA [6]. Other recent studies have also identified serum albumin as an independent predictor of SSIs and PJIs [2,6–12]. Studies of 37,173 patients undergoing total knee arthroplasty (TKA) and 49,475 patients undergoing THA in the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database found that albumin < 3.5 g/dL was a stronger independent predictor of SSI and mortality than obesity [8,13]. The superficial SSI rate was 2.14% in patients with hypoalbuminemia vs. 0.71% in patients with normal serum albumin following THA and 1.27 vs. 0.64% following TKA. The deep SSI rate was 0.38% in patient with serum albumin ≥ 3.5 g/dL vs. 0.12% in patients with hypoalbuminemia following TKA and 0.71 vs. 0.27% in THA [8,13].

In the revision TJA setting, low serum albumin has also been found to be an independent risk factor for postoperative SSIs and PJIs. Yi et al. evaluated the associations between malnutrition, septic failure and acute infection occurring after revision TJAs. The nutritional parameters used were serum albumin, TLC and transferrin. They found that in the presence of one or more altered parameters, suggestive of malnutrition, that these independently associated with both chronic PJIs and acute postoperative infections [2]. Bohl et al. found that patients undergoing revision TJA with hypoalbuminemia were more than twice as likely to develop PJIs within 30 days than those with serum albumin > 3.5 g/Dl [11].

Anthropometric measures such as calf circumference, arm muscle circumference and triceps skinfold have been utilized to identify undernutrition in orthopaedic patients, but cutoffs are poorly defined and correlations with SSIs and PJIs are not well studied [14–17].

Serum albumin is the most widely studied nutritional marker in patients undergoing TJA. Due to the correlations between nutritional status and postoperative complications, patients suspected of malnurishment should have nutritional parameters evaluated prior to elective arthroplasty. However, there is currently inadequate evidence to determine whether correction of preoperative nutritional markers results in decreased rates of SSIs and PJIs.

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1.2. PREVENTION: RISK MITIGATION

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QUESTION 1: What preoperative screening for infections should be performed in patients undergoing revision hip or knee arthroplasty because of presumed aseptic failure?

RECOMMENDATION: In addition to taking a thorough history, obtaining radiographic imaging and performing a physical examination, all patients with a failed hip or knee arthroplasty awaiting revision surgery should have their serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) measured. Patients with high index of suspicion for infection should be considered for further workup.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

While there are many etiologies that can cause pain and failure following total joint arthroplasty (TJA), infection is the most common cause of failure in total knee arthroplasty (TKA) and the third most common cause of failure in total hip arthroplasty (THA) [1,2]. The evaluation of patients with a painful TJA begins with a thorough history, physical examination and joint-specific radiographic imaging.

Patients with recent bacteremia, prolonged drainage after surgery, multiple surgeries on the same joint, history of prior periprosthetic joint infections (PJIs), history of surgical site infections of the same joint, comorbidities resulting in an immunocompromised state (i.e., diabetes mellitus, inflammatory arthropathy, etc.) or patients with increased risks of skin barrier penetrations (i.e., intravenous drug abuse, skin ulceration, chronic venous stasis, etc.) should be considered at higher risk for PJIs [3]. Physical exam findings suggestive of PJIs include joint erythema, warmth or large atraumatic effusion.

Plain radiographs should be obtained for all patients presenting with a painful TJA. It is useful to compare serial radiographs. Plain radiographic findings that should increase suspicions of PJIs include signs of early loosening, early osteolysis, periosteal elevation and transcortical sinus tract [4,5]. However, it is important to note that radiographs are rarely diagnostic of PJIs, and can often be normal in the setting of infection.

Infection can be an occult cause of pain following TJA. Therefore, screening for PJIs should be performed in every patient with a painful hip or knee arthroplasty. A successful screening test should have high sensitivity, be widely available and cost-effective. Serum inflammatory markers have been a cornerstone for screening for PJIs in the painful TJA [3–9]. Obtaining an ESR and CRP have proven to be effective screening tools for PJIs due to their high sensitivity, wide availability and cost-effectiveness [10–18]. Using ESR and CRP in combination improves sensitivity and negative predictive values [10,13,14,17–20].

It is important to note that ESR and CRP levels below established thresholds do not definitively exclude the possibility of PJIs [10,13,20]. This is especially true of patients with slow growing organisms such as *Cutibacterium acnes* (*C. acnes*) [21]. It is also true that patients with elevated serological markers do not definitely have PJIs. It is recommended that in the presence of elevated serology and/or high, clinical suspicion for PJIs, even in the presence of normal serology, joint aspiration be performed [3,5,7].

There are some additional limitations to screening using inflammatory markers. ESR, especially, and CRP are normally elevated in the early postoperative periods. Patients with elevated metal ion levels can also present with elevated ESR and CRP levels creating a clouded diagnostic picture [9]. In an effort to overcome these shortcomings, other serum biomarkers have been studied for the diagnosis of PJIs. Interleukin-6 (IL-6) is a cytokine produced by activated monocytes, macrophages and T-cells and has been shown to be a highly-sensitive and specific biomarker for PJIs. However, selection bias, cofounding variables and small study sizes have limited its wide spread adoption [11,22–24]. In a recent study, Shahi et al. evaluated serum D-dimer (fibrinolytic by-product) as a marker of PJIs. In their study, D-Dimer outperformed both ESR and CRP individually and when combined in terms of sensitivity and specificity for diagnosis of PJIs [20]. While promising, this was the first study to analyze the role of D-dimer in diagnosing PJIs.

It is clear that there is a need for more specific and accurate serological screening tests in order to diagnose PJIs. The future holds

promise as the role of new serological markers are being evaluated. Until a more accurate serum marker is introduced, we recommend that any patient with suspected diagnosis of PJI be screened using serological tests for inflammation, namely, CRP and ESR. Consideration should also be given to testing D-dimer as a potential supplementary serological test.

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QUESTION 2: Does prior septic arthritis (aerobic, anaerobic, fungal, tuberculosis) of a native joint predispose the patients to an increased risk of subsequent periprosthetic joint infection (PJI) in the same joint receiving arthroplasty? If yes, how soon after a prior septic arthritis can elective arthroplasty be performed in the same joint?

RECOMMENDATION: Yes. A prior septic arthritis in a joint does predispose the same joint to subsequent PJI after arthroplasty. In the absence of concrete evidence, we recommend that arthroplasty be delayed at least until completion of antibiotic treatment and resolution of clinical signs of infection, but no earlier than three months from the inciting event.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 87%, Disagree: 9%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

The role of total joint arthroplasty (TJA) in patients with prior septic arthritis is not clearly defined. The number of variables involved in such cases have made all current, cohort-based studies difficult to statistically compare. These variables include, age of onset of septic arthritis (child vs. adult), septic joint with or without osteomyelitis involvement, type of joint infected (knee vs. hip), operation performed (one-stage vs. two-stage), time between septic joint and TJA or time between stages for two-stage procedures, and the initial organism causing septic arthritis (tuberculosis vs. bacterial). These variables, among others, are important because they contribute to substantial heterogeneity between patients being treated under the blanket term of having prior septic arthritis.

Previous studies have often grouped patients with differing amounts of these variables together and have reported low-powered and inconclusive results. We performed a systematic review of the literature [1–51] including studies that have directly compared this patient population to those undergoing primary TJA at the same institution by the same surgeons to assess whether or not patients

with prior septic arthritis are at an increased risk of PJIs [39]. A case-control study of 36 total patients (18 in each cohort) found no significant differences in the infection rates between patients undergoing TJA for osteoarthritis and those who had prior septic arthritis [39]. This study was limited by its small size and, as the authors suggest, larger studies are needed to make an accurate statement about the comparative PJI rates.

In the largest published series to-date, Kim et al. reviewed 170 patients (85% infected with *Staphylococcus aureus*) undergoing one-stage total hip arthroplasty (THA) with quiescent infection (mean 33 years post-infection), all of which had septic arthritis in childhood [30]. In this series, all patients, except for one (two hips), had THA at least 10 years after septic arthritis and the only hips that were complicated by PJIs after THA were those two hips that had a quiescent period of seven years. The authors recommended that a 10-year quiescent period be the minimum required to undergo THA after septic arthritis [30]. In contrast, another large cohort by Seo et al. reported on 62 patients (42% methicillin-resistant *Staphylococcus* species) undergoing one-stage total knee arthroplasty (TKA) after a mean quiescent period of only 4 years, all of which had adult-onset septic arthritis with a PJI rates of 9.7% [43]. Jerry et al. evaluated 65 patients (20 with osteomyelitis and 45 with septic arthritis) undergoing one-stage TKA with an average quiescent period in both groups of 18 years [25]. The series reported PJI rates of 15% in the osteomyelitis cohort and 4% in the septic arthritis group [25]. All of these studies demonstrate the heterogeneity of the current literature on this topic.

In patients undergoing THA for tubercular arthritis, the recommended periods of quiescence before THA varies from immediate to 10 years [29,38,46]. However, reactivation has been reported even in cases operated on after a quiescent period of 37 to 40 years [50]. Hence, as a part of preoperative assessment, only patients who had completed a full course of antitubercular treatment (ATT) therapy were considered for THA. A recent systematic review of THA in tuberculosis of the hip by Tiwari et al. [51] concluded that ATT be given for at least two weeks preoperatively and continued for 6 to 18 months postoperatively to minimize reactivation rates. The study also indicated that patients with draining sinuses should be disqualified from undergoing one-stage THA and should instead undergo a two-stage procedure [51].

Because of the limitations of the current literature, the statistical analyses performed on these studies at this time has been restricted to pooled, weighted infection rates inclusive of 1,300 TJAs (Table 1). In order to address the heterogeneity problem, we have subdivided the cohort into subgroups including one-stage and two-stage procedures, adult onset septic arthritis and childhood (< 18 years) onset septic arthritis, etc. This data demonstrates a PJI rate of 8.26% for TKAs and a 5.20% rate for THAs, while both bacterial septic joint and tuberculous septic joint achieved PJI rates around 6%. Next, we subdivided the cohort by the treatment type (one-stage vs. two-stage procedures) and then performed the analyses by further dividing each of these two groups (Table 2). Weighting and pooling the data this way allowed for more homogenous analyses, but further divisions within each of these cohorts were not possible due to sample size limitations. As mentioned, comparative statistics were not possible on these infection rates due to limitations in individual study designs.

To conclude, patients with prior septic arthritis undergoing TJA in the same joint have an increased rate of infection compared to patients undergoing primary TJA without prior septic arthritis. The following recommendation is based on the limited data currently available: management of septic arthritis by arthroplasty using the following protocol (two-stage TJA in the case of active/evolving arthritis and one-stage TJA in the case of quiescent arthritis) may yield good functional results. This is the only study to date directly comparing the one- and two-stage TJAs demonstrating infection control rates of up to 87% in active/evolving septic arthritis and up to 95% in quiescent arthritis [11]. The literature still lacks appropriately-sized, randomized clinical trials or prospective, comparative case-control studies to better support these recommendations.

TABLE 1. PJI rates for TJA following prior septic arthritis of same joint

Pooled Cohort Type (n)	PJI Rate (Same Joint)	95% CI
All studies, pooled (n=1300)	5.96%	4.24 to 7.94
One-Stage TJA, pooled (n=1020)	5.14%	3.31 to 7.36
Two-Stage TJA, pooled (n=280)	8.70%	5.77 to 12.49
Bacterial Septic Joint, pooled (n=977)	5.84%	3.97 to 8.05
TB/mycoplasma Septic joint, pooled (n=323)	6.09%	2.94 to 10.28
Adult-onset Septic Joint, pooled (n=717)	8.35%	6.48 to 10.55
Childhood-onset Septic Joint, pooled (n=583)	2.18%	1.16 to 3.70
Hip Septic Joint to THA, pooled (n=1037)	5.20%	3.50 to 7.21
Knee Septic Joint to TKA, pooled (n=263)	8.26%	5.30 to 12.15
Total Primary TJA (from literature) [1-6]	0.4%-1.5%	NA

PJI, periprosthetic joint infection; TJA, total joint arthroplasty; CI, confidence interval; TB, tuberculosis; THA, total hip arthroplasty; NA, not available

TABLE 2. Infection rates by stage, subdivided by groups to decrease heterogeneity

	All Septic Arthritis to TJA (n=1300)							
	One-stage Procedure				Two-stage Procedure			
Age at SA	Adult Onset (n = 437)	95% CI	Child Onset (n = 583)	95% CI	Adult Onset (n = 280)	95% CI	Child Onset (n = 0)	95% CI
PJI rate	8.12%	5.78 to 11.01	2.18%	1.16 to 3.70	8.70%	5.77 to 12.49	NA	NA
Infection type	TB (myco) (n = 314)	95% CI	Bacterial (n = 706)	95% CI	TB (myco) (n = 9)	95% CI	Bacterial (n = 271)	95% CI
PJI rate	6.32%	2.97 to 10.82	4.54%	2.51 to 7.13	0.00%	NA	8.98%	5.95 to 12.88
Procedure	THA (n = 807)	95% CI	TKA (n = 213)	95% CI	THA (n = 230)	95% CI	TKA (n = 50)	95% CI
PJI rate	4.08%	2.36 to 6.23	8.62%	5.27 to 13.12	9.14%	5.83 to 13.49	6.91%	1.86 to 16.98

TJA, total joint arthroplasty; SA, septic arthritis; CI, confidence interval; PJI, periprosthetic joint infection; TB, tuberculosis; THA, total hip arthroplasty; TKA, total knee arthroplasty; NA, not available

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QUESTION 3: What indicators/metrics would compel a surgeon to perform resection arthroplasty and antibiotic spacer insertion, delaying the arthroplasty to a later date, in a patient with prior septic arthritis undergoing primary arthroplasty?

RECOMMENDATION: Patients with active septic arthritis or chronic osteomyelitis of the hip or knee may be best treated with a two-stage arthroplasty. Evidence would suggest a limited risk of infections recurrence following a one-stage arthroplasty in the presence of a quiescent septic arthritis.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 85%, Disagree: 11%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Although degenerative joint diseases are a common sequela of septic arthritis in a native hip or knee, the incidence of septic arthritis is relatively low. Therefore, orthopaedic surgeons are not regularly confronted with the difficult decision regarding the treatments of degenerative joint disease in patients with prior septic arthritis. Due to the low incidence, we are confronted with a paucity of literature to guide our treatment decisions.

In the reporting of outcomes, the literature has differentiated between active and quiescent septic arthritis/osteomyelitis of the hip or knee. Patients with quiescent septic arthritis/osteomyelitis often had a distant history of infections and the investigation of serum, synovial aspirate and imaging studies demonstrated no signs of active infections. Given the differentiation made in the literature, we have reviewed the two different hip and knee patient populations.

Among the reporting of total hip arthroplasties (THAs), seven publications with 98 hips and nine publications with 398 hips were identified as reporting on active or quiescent hip septic arthritis/osteomyelitis, respectively (Table 1). All reports of active hip infections were only treated with a two-stage arthroplasty, which demonstrated a 10.2% recurrence of infection. Unlike the active hip infections, all quiescent hip infections were treated with a one-stage arthroplasty with a 1.5% recurrence of infection.

Even fewer publications were available on total knee arthroplasties (TKA), which had seven publications with 46 knees and five publications with 89 knees reporting on active and quiescent knee septic arthritis/osteomyelitis, respectively (Table 2). Among the reports of active knee infections, all but three knees were treated with a two-stage arthroplasty demonstrating a 4.7% recurrence of infection, while the three knees treated with a one-stage arthroplasty had no recurrences. Similar to quiescent hip infections, all quiescent knee infections were treated with a one-stage arthroplasty and had a 4.5% recurrence of infection.

The literature suggests performing routine two-stage arthroplasty for active infections at the time of arthroplasty and one-stage arthroplasty for quiescent infections at the time of arthroplasty. Although the rates of infections are relatively low utilizing these parameters, there is conversely limited data about the failure rates after one-stage arthroplasty with an active infection and no data about two-stage arthroplasty for quiescent infections. As a result, it is possible that these recommendations could change with additional future research.

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TABLE 1. Publications reporting on active and quiescent hip septic arthritis/osteomyelitis

Lead Author, Year	Infection Classification (Active vs. Quiescent)	Procedure (One- vs. Two-stage)	Number of Hips	Average Follow-up Duration (Months)	Number of Infection Recurrence
Kim (2003)[1]	Quiescent	One-stage	170	119	2
Park (2005)[2]	Quiescent	One-stage	75	70	1
Lustig (2007)[3]	Quiescent	One-stage	17	72	1
Chen (2008)[4]	Active	Two-stage	28	77	4
Kim (2009)[5]	Quiescent	One-stage	62	156	1
Yoo (2009)[6]	Quiescent	One-stage	38	100	1
Gao (2010)[7]	Quiescent	One-stage	19	34	0
Bauer (2010)[8]	Active / Quiescent	Two-stage / One-stage	13 / 9	60	2 / 0
Huang (2010)[9]	Active	Two-stage	15	42	0
Fleck (2011)[10]	Active	Two-stage	10	28	1
Shen (2013)[11]	Active	Two-stage	5	40	0
Anagnostakos (2016)[12]	Active	Two-stage	16	45	3
Papanna (2017)[13]	Active / Quiescent	Two-stage / One-stage	11 / 7	70 / 72	0 / 0

TABLE 2. Publications reporting on active and quiescent knee septic arthritis/osteomyelitis

Lead Author, Year	Infection Classification (Active vs. Quiescent)	Procedure (One- vs. Two-stage)	Number of Knees	Average Follow-up Duration (months)	Number of Infection Recurrence
Böhler (2000)[14]	Active	One-stage	3	15	0
Lee (2002)[15]	Quiescent	One-stage	20	60	1
Nazarian (2003)[16]	Active	Two-stage	14	54	0
Bae (2005)[17]	Quiescent	One-stage	32	120	2
Kirpalani (2005)[18]	Active	Two-stage	5	38	0
Bauer (2010)[8]	Active / Quiescent	Two-stage / One-stage	17 / 14	60	2 / 1
Ashraf (2013)[19]	Active	Two-stage	2	30	0
Chen (2013)[20]	Quiescent	One-stage	22	Unreported	Unreported
Hochreiter (2016)[21]	Active	Two-stage	2	12	0

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QUESTION 4: Does a prior arthroscopy of the hip joint increase the risks of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing elective total hip arthroplasty?

RECOMMENDATION: There is no evidence to suggest that a prior arthroscopy of the hip increases the risk of subsequent SSIs/PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 81%, Disagree: 11%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

The use of hip arthroscopy for the treatment of various intra-articular or extra-articular problems has gained popularity during last decade [1,2]. Hip arthroscopy is known to be a safe and effective method for the treatment of femoroacetabular impingement (FAI) [3,4]. It is assumed, that the arthroscopic management of impingement or labral pathology will delay the process of joint degenerative disease. However, a considerable number of patients with both conservatively and arthroscopically-managed FAI eventually undergo total hip arthroplasty (THA) [5,6]. A second surgery, on a previously operated hip, could be complicated by scar formation and changes in neurovascular anatomy. In addition, potential contamination of the hip during hip arthroscopy could potentially predispose the patient to SSIs/PJIs after THA.

Several studies have evaluated the functional and clinical outcomes of THA after ipsilateral hip arthroscopy [7–12]. All of the studies on this subject were case-control studies, largely focusing on functional and clinical outcomes. The available studies did not have sufficient patient numbers to determine the risk of SSIs/PJIs following previous arthroscopy. Zingg et al. [7] compared three groups of patients. One group consisting of 18 patients who underwent THA after previous ipsilateral hip arthroscopy, compared with two control groups with a minimum of one-year follow-up. One control group received identical approach and implants; and the other a paired group matched for age, Body Mass Index (BMI) and Charnley categories. In their case cohort, only one patient had a superficial wound infection due to a suture granuloma that resolved with antibiotic therapy. They reported that previous hip arthroscopy would not negatively influence the performance or short-term clinical outcome of THA.

Nam et al. [12] compared 43 patients who received hip resurfacing arthroplasty following previous hip arthroscopy to a 1:2 matched group of 86 controls. Various clinical and functional outcomes were evaluated at different time points of six weeks, three months, six months, one year, and most recent follow-up visits. No ultimate differences were reported in functional scores, range of motion or complications, including infection at final follow-up.

Haughom et al. [10], evaluated 42 hips who underwent THA after a previous hip arthroscopy at a mean follow-up of 3.3-years and compared them to an age, sex and BMI (1:2) matched cohort of primary THAs. No significant difference was observed in postoperative Harris Hip Scores (HHS), rates of complications or revisions. One patient in each group had a PJI and underwent a subsequent revision.

Charles et al. [9], compared 39 patients who underwent THAs after hip arthroscopy to a 1:1 group of patients matched for age, sex and body mass index who underwent THA without prior hip arthroscopy. The groups had no statistically significant differences in terms of postoperative superficial or deep periprosthetic infections at a minimum 1-year follow-up (mean 52 months).

In a recent study, Perets et al. [11], compared 35 THA patients with a history of prior hip arthroscopy to a group of 1:1 matched controls. The matching criteria were age, sex, body mass index, surgical approach and robotic assistance. They evaluated the Harris Hip Scores (HHS), Forgotten Joint Score-12, Visual Analog Scale (VAS), satisfaction, postoperative complications, and reoperation rates following a minimum two-year follow-up. In the case group, 2 patients (5.7%) had minor infections which were managed nonoperatively compared to zero infections/complications in the control

group. Although the prior arthroscopy group had higher rates of both complications (n = 5, 14.3%) and reoperations (n = 4, 11.4%), only the difference in total complications approached marginal significance (p = 0.054). Complications consisted of urinary tract infection, numbness around the incision, minor infection and allergic reaction to sutures.

With the current evidence available, we cannot conclude that a prior hip arthroscopy exposes patients undergoing THAs to a higher risk of infections. There is a need for studies with greater sample sizes to further explore this important question.

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QUESTION 5: Does a prior arthroscopy of the knee increase the risk of subsequent surgical site infections/periprosthetic joing infections (SSIs/PJIs) in patients undergoing elective arthroplasty?

RECOMMENDATION: There is no evidence to suggest that a prior arthroscopy of the knee increases the risk of subsequent SSIs/PJIs in patients undergoing total knee arthroplasty (TKA).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 81%, Disagree: 12%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Arthroscopy in the degenerate knee is not warranted, but it has been frequently performed over the years. Controversial indications have included young adults with degenerative joint disease to delay TKA [1,2] and for elderly patients for alleviating pain [3,4]. Knee arthroscopy can be appropriately used for loose body removal, meniscectomy, chondroplasty, ligamentous reconstruction and as a diagnostic tool prior to unicondylar knee arthroplasty [5]. The rate of TKA following knee arthroscopy within one year is 10-12% [6–8], and those following ligamentous knee surgery have a higher risk of earlier osteoarthritis requiring TKA [9]. Studies have shown increased risks of revisions and PJIs after TKAs in patients with previous open-knee procedures [10–12], but the evidence for knee arthroscopy is conflicting.

Piedade et al. evaluated the outcomes and complications of TKAs in two retrospective cohort studies [11,13]. The first was a cohort of 1,119 primary TKAs with no previous surgery compared to 60 primary TKAs with a prior history of arthroscopic debridement and a minimum follow-up of two years. Two patients in the arthroscopy group (3%) and 14 patients in the primary TKA group (1.25%) had subsequent PJIs. Although this finding was not statistically significant, the total complication, reoperation and revision TKA rates were higher in the prior arthroscopic group. In addition, the authors found no correlations between arthroscopy-TKA intervals (mean of four years) and complications or failures [11]. The second study did not specify the rates of infections [13]. When looking at general outcomes, Issa et al. reported no negative outcomes (function, survivorship and revision) following TKA after prior knee arthroscopy [14].

The time interval between arthroscopy and TKA is also important as was shown by Werner et al. [8], who evaluated the associations of knee arthroscopy prior to TKA with postoperative complications (infection, stiffness and venous thromboembolism) from a national database. Three cohorts were compared with each other and with an age-matched cohort. The three cohorts were: TKA within 6 months (n = 681), between 6 to 12 months (n = 1,301) and between 1 to 2 years after knee arthroscopy (n = 1,069). They reported that TKAs performed within 6 months were associated with increased rates of postoperative infection, stiffness and venous thromboembolism.

Viste et al. [6], evaluated long-term Knee Society Scores (KSS), survivorships and complications of 160 TKA patients with prior knee arthroscopy (excluding ligamentous reconstruction) to a 1:2 matched control group of 320 primary TKAs with no prior surgery. The mean follow-up was nine years and the mean interval between arthroscopy and TKA was five years. Although PJIs were found in two controls and three arthroscopy cases, these findings were not statis-

tically significant (p = 0.2). In addition, there were no significant differences between the two groups regarding complications, ranges of motion and revisions. Twenty-five patients (15.6%) had a knee arthroscopy within one year of their TKA during which time there were no increased risks of infections, other complications, reoperations or revisions.

A national registry database study of 64,566 primary TKAs found that prior ligament reconstruction (odds ratio (OR) = 1.85) was an independent risk factor for PJIs at 12 months in multivariate analysis, with no details of whether this was open or arthroscopic. Interestingly, meniscectomy was an independent protective factor (OR = 0.66) in the same study [15].

We conclude that a prior arthroscopy of the knee does not seem to increase the incidence of subsequent SSIs/PJIs following TKA. However, most studies on this subject are retrospective with small cohorts, making it difficult to accurately assess the risk of subsequent infection. Only one study showed an increased rate of infection within six months, and this has not been repeated in the literature. Further studies are required, and until then, surgeons may wish to consider delaying TKA for at least six months post-arthroscopy to minimize any risk that may exist, particularly in high-risk patients.

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QUESTION 6: Do patients undergoing outpatient total joint arthroplasty (TJA) have a higher incidence of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: No. Patients undergoing outpatient total joint arthroplasty do not have a higher incidence of SSIs/PJIs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 83%, Disagree: 8%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

PJIs are a serious condition with a high impact on patients and surgeons. The leading cause of 30-day readmission after total knee arthroplasty (TKA) is deep or superficial SSIs, which accounts for 12.1% of unplanned readmissions [1]. SSIs accounted for 23.5% of unplanned readmissions in total hip arthroplasty (THA) patients, just behind hip dislocations. Lovett-Carter et al. reported that the length of hospital stay (LOS) is implicated as a risk factor for SSIs or PJIs, among other factors such as comorbidities, gender and duration of procedure [2]. Outpatient TJA has not been seen to be a concern in the literature.

In a study that evaluated 58,000 standard-stay, primary THA patients, the deep SSI rate was seen to be 0.2% [3]. In a more recent study, Lovett-Carter et al. evaluated outpatient 742 THAs and 816 TKAs and observed 0 and 3 (0.36%) SSIs, respectively [2].

Nelson et al. revised the collected data from the 2005 to 2014 American College of Surgeons National Surgical Quality Improvement Database (ACS NSQIP) of patients who underwent THA as outpatient (LOS 0 days) or inpatient (LOS 1-5 days). A total of 63,844 THA patients were identified of which 420 (0.66%) were outpatients. They concluded that patients undergoing outpatient THA were not at an increased risk of 30-day adverse events or readmissions or infections compared to inpatient procedures. Deep SSIs in patients with LOS between 1 to 5 days was 0.23% and in outpatients was zero (p = 0.319). The rate of superficial SSI was 0.64 vs. 0.48% (p = 0.821), respectively [4].

Springer et al. compared 30-day hospital readmission rates for patients undergoing outpatient and inpatient TJAs. They evaluated if LOS impacted hospital readmission rates and unplanned care

TABLE 1. ACS NSQIP database comparison of complications within 30 days of surgery between the outpatient and inpatient TJA groups [7]

SSI	Outpatient: N = 1,220	Inpatient: N = 168,186
Superficial	6 (0.5%)	1.053 (0.6%)
Deep	4 (0.3%)	354 (0.2%)

episodes. The group found that there was only 1 case of hospital readmission out of 137 patients due to infection in the outpatient group (0.7%), and none of the 106 patients in the inpatient group had any unplanned care episodes [5]. They concluded that no statistical differences were seen in 30-day readmission or unplanned care episode. Kolisek et al. compared the results of two selected matched cohorts of 64 patients who underwent TJA during the same period, and found two cases of SSIs in the inpatient group vs. zero in the outpatient cohort [6]. Courtney et al. determined that the complications associated with outpatient vs. inpatient TJA seen in the ACS NSQIP database were not significant, specifically in superficial and deep SSIs [7].

When comparing costs, complications and mortality between outpatient TKA patients and those who had a 3 to 4 night hospital stay, Lovald et al. determined that the SSI rate was not different at 1.9 and 2.0% respectively [8]. Furthermore, Goyal et al. performed a multicenter, randomized control study, comparing patients undergoing THA as inpatients (108) and outpatients (112). They showed no differences in SSI rates, 0.92% and 0.89% respectively, at four weeks follow-up [9]. Klein et al. reported 5 infections (0.9%) in 549 THAs as outpatient with a follow-up of 90 days [10]. Berger et al., with the same follow-up, evaluated 25 unicondylar knee arthroplasties and 86 TKAs as outpatient surgeries and found only one irrigation and debridement [11]. Bovonratwet et al. compare 956 inpatient TKAs with 642 outpatients in a follow-up of 30 days and found SSI rates of 0.85 and 0.78% respectively [12].

Only one retrospective, database study by Arshi et al. showed different findings than the studies mentioned above. They compared 4,391 outpatient TKAs vs. 128,951 inpatient TKAs and saw a significant difference in SSI incidences of 1.21% and 0.91% respectively [1]. They concluded that data from a private insurance database demonstrated higher risks of perioperative surgical and medical complications, including, component failure, SSI, knee stiffness and deep vein thrombosis. However, it should be noted that this study did have selection bias for their patients, and was extracted from a database that could potentially add bias.

Basques et al. reviewed the ACS NSQIP database for comparisons between same-day discharge and inpatient hospitalizations of elective hip and knee arthroplasty cases in terms of postoperative complications and 30-day readmission rates [13]. This study was comprised of 1,236 same-day surgery cases that were identified from their institution, and matched to the same number of cases from the database. Same-day cases were found to have higher readmission rates and returns to the operating room. In particular, infections were the most common cause for readmissions and returns to the operating room. On the other hand, the inpatient group had a higher incidence of thromboembolic events. These higher readmission rates were seen specifically for patients in the same-day surgery TKA group. The risk factors for 30-day readmissions following same-day procedures include BMI > 35 kg/m^2, diabetes and age > 85 years.

In conclusion, based on available data, performing TJA in an outpatient setting does not seem to predispose patients to a higher incidence of SSIs/PJIs.

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1.3. PREVENTION: ANTIMICROBIALS (SYSTEMIC)

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QUESTION 1: What is the most appropriate perioperative prophylactic antibiotic (agent, route and number of doses) for patients undergoing primary total joint arthroplasty (TJA) to reduce the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: The most appropriate perioperative prophylactic antibiotic is a first or second-generation cephalosporin (i.e., cefazolin or cefuroxime) administered intravenously within 30 to 60 minutes prior to incision as a single- and weight-adjusted dose.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 90%, Disagree: 8%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

The optimal prophylactic antibiotic should be a bactericidal agent against the most common organisms responsible for causing SSIs/PJIs. The agent must be present within the tissues at the time of initial incision, with adequate serum concentrations above the minimum inhibitory concentration (MIC) and should be maintained during the procedure [1,2]. A first- or second-generation cephalosporin (i.e., cefazolin or cefuroxime) can be used for routine perioperative prophylaxis with excellent distribution and cost effectiveness. The American Academy of Orthopaedic Surgeons (AAOS) currently recommends the use of either of these two agents in patients undergoing any orthopaedic procedure including TJA [3]. Prophylaxis should target the most common organisms (i.e., *Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli,* and *Proteus*) while avoiding unnecessary broad-spectrum therapies [4]. Glycopeptides, such as teicoplanin and vancomycin, have also been introduced as reasonable alternatives, although they have a narrower spectrum of action with minimal activity against gram-negative bacteria [5–7].

Vancomycin is selectively used in patients, such as nursing home residents and healthcare workers, who are MRSA carriers or at high-risk of MRSA colonization. In patients with documentation or suspicion of an allergy to cephalosporins, clindamycin can also be utilized and should be administered within one hour of the surgical incision. Vancomycin should be started two hours prior to incision due to the extended infusion time [8,9]. Although alternative agents such as vancomycin have been suggested in cases of allergies to cephalosporins, these have been associated with higher rates of SSIs if used alone [10–12]. In the study by Courtney et al., the authors reported that the addition of vancomycin to the prophylactic antibiotic regimen does not decrease the rates of SSIs, when compared with cefazolin alone, and could increase the risks of adverse effects [12]. Without clear evidence, the superiority of dual-antibiotic prophylaxis in prevention of infection should be carefully considered.

Bosco et al. [13] evaluated the increasing prevalence and virulence of gram-negative pathogens as these were the causative pathogens in up to 30% of infections in total hip arthroplasty (THA). They instituted the Expanded Gram-Negative Antimicrobial Prophylaxis (EGNAP) for hip arthroplasty patients. Two groups were compared in terms of SSI rates; one group did not receive weight-based, high-dose gentamicin while the second group did. The reported rates were 1.19 vs. 0.55% after EGNAP was implemented ($p = 0.05$). On a different study, Tan et al. [14] specifically evaluated the influence of comorbidities and use of perioperative antibiotics in 1,022 patients with PJIs to determine the influence of comorbidities on organism profile. They found that no comorbidities were associated with an increased rate of gram-positive or gram-negative infections. Their results support the current recommendations of a universal antibiotic prophylaxis protocol rather than an antibiotic regimen individualized to a patient's comorbidities.

Malhas et al. [15] examined microbiological results from hip and knee revisions from 2001 to 2010. Antibiotic resistance patterns were evaluated on *Staphylococcus aureus* (SA) and coagulase-negative *Staphlococcus* (CNS) cultured from regional pan-speciality sources. A total of 72 revisions in 67 patients were included. The most common organisms were SA (36%) and CNS (35%). Resistance to methicillin was 72 for CNS vs. 20% for SA and resistance to gentamicin was 40% for CNS vs. 4% for SA. Among all regional (background pan-speciality) cultures, SA resistance to methicillin fell from 32 to 16% from 2006 to 2010 with no change in gentamicin resistance at 3%. During the same period, resistance of CNS to methicillin and gentamicin increased from 63 to 70% and 32 to 47%, respectively. The prophylaxis regimen prior to 2008 was cefuroxime, and after 2008 was gentamicin and flucloxacillin.

Other Agents

Flucloxacillin and gentamicin: Torkington et al. [16] investigated bone penetration of intravenous antibiotic prophylaxis with flucloxacillin (2 gm) and gentamicin (3 mg/kg) single doses during hip (18 patients) and knee (21 patients) arthroplasty, and their efficacy against *S. aureus* and *S. epidermidis*. This study demonstrated that the intravenous antibiotic prophylaxis combination of flucloxacillin and gentamicin achieved adequate concentrations in bone against the common causative organisms in total knee arthroplasty (TKA) and total hip arthroplasty (THA) PJIs, adding to the available evidence to support its use.

Teicoplanin: Four randomized controlled trials provided strong evidence for the use of a single dose of 400 mg of teicoplanin at induction in selected cases [17,18]. Although there is no evidence to suggest that higher doses or prolonged courses of treatments result in fewer SSIs, studies have shown that this dose may be inadequate for patients weighing over 70 kgs [19].

Sulbactam-ampicillin: Yuasa et al. [20] compared the incidence of SSIs with two doses of sulbactam-ampicillin after THA: 1.5 and 3 grams. They found a global decrease in SSIs in the 3 gm dose group from 2.91 to 1.08% ($p = 0.268$), and in deep infection from 1.2 to 0% ($p = 0.231$).

Cloxacillin vs. clindamycin: Robertson et al. compared the risks of PJIs between the use of cloxacillin and clindamycin as perioperative antibiotics in 80,018 TKAs. The risk of failure leading to revision due to PJI was higher with clindamycin compared to cloxacillin (risk ratio (RR) = 1.5, 95% confidence interval (CI): 1.2 to 2.0; $p = 0.001$). Clin-

damycin inhibits bacterial protein synthesis by binding to bacterial 50S ribosomal subunits and it may be bacteriostatic- or bactericidal-based on the organism and drug concentration. Cloxacillin is in the beta-lactam category and works by binding to specific penicillin-binding proteins located inside the bacterial cell wall which inhibit cell wall synthesis. The primary reason for using clindamycin as a perioperative prophylaxis antibiotic is a reported allergy to penicillin. Even though between 5 and 10% of hospitalized patients report allergy to penicillin, most have negative results when tested for type-I hypersensitivity [21].

Dose

Current guidelines and studies recommend giving universal antibiotic prophylaxis to all TJA patients regardless of their medical conditions or immune status [2,3,14]. We did not identify studies that showed consistent reports on prophylactic dosage. Clinical practice guidelines, based on available evidence and expert opinion, recommend increasing the single preoperative prophylactic antimicrobial agent dose for select prophylactic antimicrobial agents in overweight and obese patients. For cefazolin, recommendations are to administer 2.0 gm for patients weighing > 60-80 kg and 3.0 gm if > 120 kg. For aminoglycosides, dosing is calculated using the patient's ideal body weight plus 40% of the difference between the actual and ideal body weight. Vancomycin should be dosed at 15 mg/kg. The goal of dosing is to achieve a safe and effective tissue concentration of the drug that sufficiently exceeds the concentration needed to inhibit the growth of most colonizing skin flora at the time of surgical incision [2,7].

Angthong et al. [22] found that IV cefazolin at a dose of 2 gm produced greater intraosseous concentrations overall than a dose of 1 gm. However, the higher intraosseous concentrations did not correlate with higher inhibitory effects. A second study demonstrated that biofilm formation could develop for up to 1–2 days [12]; therefore, hypothetically, the higher dose (2 gm) of cefazolin might be more beneficial than the lower dose of 1 gm [22].

Redosing: Moderate-quality evidence suggested no benefits of intraoperative antibiotic redosing. Clinical practice guidelines, based on a review of the evidence and expert opinion, recommend prophylactic antimicrobial agent redosing in cases of prolonged procedures (when the procedure exceeds the half-life of the prophylactic antimicrobial agent or is longer than 3 to 4 hours) and in patients with major blood loss (> 1,500 ml) or extensive burns. Redosing should also be performed at intervals of 1 to 2 times the prophylactic antimicrobial agent half-life, starting at the beginning of the preoperative dose [2].

Route

The best route to deliver antibiotics prior to total joint arthroplasty is considered to be intravenous in order to reach levels above MIC. Therapeutic concentrations should be maintained for the duration of the surgical procedure. Recent publications have suggested alternate routes such as intraosseous administration, although further research is required [1]. Irrigation solutions with antibiotics have also been used with little or no evidence. Among the few available low-evidence studies, Whiteside reported his experience in 2,293 arthroplasties using an irrigation solution of normal saline with vancomycin 1,000 mg/l and polymyxin 250,000 units/L at 2 L/hour. No patients required readmission for primary infection or further antibiotic treatment [23]. However in a meta-analysis study evaluating the use of topical antibiotic in colo-rectal surgery, no benefit was identified when used in conjunction with systemic antibiotics [1]. At present, the use of topical antibiotics, in conjunction with systemic antibiotics for prophylaxis in total joint arthroplasty, remains unproven.

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QUESTION 2: What are the appropriate weight-adjusted prophylactic antibiotic dosages?

RECOMMENDATION: The recommended weight-adjusted doses of antimicrobials for prophylaxis of hip and knee arthroplasty in adults are shown in Table 1.

TABLE 1. Recommended weight-adjusted doses of antimicrobials for prophylaxis of hip and knee arthroplasty in adults

Antimicrobial	Recommended Dose	Re-dosing Interval
Cefazolin	2 gm (consider 3 gm if patient weight ≥ 120 kg*)	4 hours
Vancomycin	15-20 mg/kg*	Not applicable
Clindamycin	600-900 mg#	6 hours

*Actual body weight.
#No recommended adjustment for weight.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 4%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

We performed a systematic review in order to examine the literature and determine appropriate weight-adjusted prophylactic antibiotic doses for the prevention of infections after hip and knee arthroplasties. The nature of the question and the lack of high-quality evidence did not allow a formal systematic review. We searched for larger comparative studies or systematic reviews where different doses of antibiotics or different antibiotics are being compared or smaller prospective pharmacokinetic/tissue penetration studies where antibiotics doses are recorded. We included studies examining systemic (not local) antimicrobials and where the antimicrobial was given for a primary or revision hip or knee arthroplasty procedure and no other procedures (e.g., dental procedure) with a prosthetic joint *in situ*.

Perioperative antimicrobial prophylaxis for patients undergoing orthopaedic procedures is routinely administered and is believed to be one of the most important steps for prevention of surgical site infections/periprosthetic joint infections (SSIs/PJIs). Cephalosporins are believed to be the most effective prophylactic agents for patients undergoing orthopaedic procedures as they have excellent bone penetration, bioavailability and a relatively extended half-life. However, in patients with allergies, a range of antimicrobials may be utilized that includes vancomycin and clindamycin.

The American Society of Health-System Pharmacists (ASHP) clinical practice guidelines provide important information regarding antimicrobial prophylaxis in surgery [1]. Doses of antimicrobials commonly used for surgical prophylaxis can be found in these guidelines. No high-quality randomized trials are investigating the safety or efficacy in preventing surgical infections of different doses of prophylactic systemic antimicrobials for surgery, including joint arthroplasty. The first International Consensus Meeting in 2013 recommended that perioperative antimicrobial prophylaxis be weight-based. These recommendations were based on the notion that the dose of antibiotic administered directly influences the serum levels of the given antimicrobial with inadequate serum levels of the antimicrobial being considered detrimental.

Serum and tissue concentrations of antimicrobials given at standard doses may not be adequate in obese patients due to various factors [2]. Pharmacokinetic studies have shown that tissue levels of cefazolin below the minimal inhibitory concentration (MIC) of common pathogenic organisms are found in body tissues near the end of surgery with a 1 gm dose [3,4]. In one small, prospective study on obese patients, a 2 gram dose of cefazolin was associated with a lower surgical site infection rates than a 1 gm dose [4]. A 2 gm dose likely achieves appropriate local surgical tissue levels, including in bone, in normal size patients [5]. However, in one study with morbidly obese patients, a 2 gm dose was associated with levels below pathogen MICs of cefazolin [6]. Given the finding of these studies, as well as the low cost and favorable safety profile of cefazolin, weight-based dosing of prophylactic cefazolin has been recommended as part of the ASHP clinical practice guideline for antimicrobial prophylaxis in surgery [1]. In this guideline, 2 gm of cefazolin is recommended as a standard dose and 3 gm for patients weighing 120 kgs or greater. Subsequent small studies [7,8], including a small randomized controlled trial [9], have compared tissue levels of 2 gm with 3 gm of cefazolin in obese women undergoing caesarean section. These have shown higher tissue levels in patients receiving 3 gm; however, 2 gm doses generally exceeded the MIC of common pathogens. Given the lack of evidence showing a clear benefit in tissue penetrations or reduced infection rates, we recommend that a 2 gm dose of cefazolin is appropriate for most patients; however, given the limited toxicity, a 3 gm dose can be considered in patients ^{3} 120kg as per ASHP guidelines.

There is some evidence to suggest that vancomycin may be more likely to achieve therapeutic serum levels with weight-based dosing of 15 to 20 mg/kg compared with a standard dose (often 1 gm) when given for surgical prophylaxis without an increased risk of renal impairment. Patients receiving appropriate weight-based dosing may have a lower rate of methicillin-resistant *Staphylococcus aureus* (MRSA) infection, however, there is no evidence suggesting an overall lower rate of infection [10–12]. In addition, weight-based dosing rather than a fixed 1 gm dose has been recommended for total joint arthroplasty [10,11]. Kheir et al. reported that a fixed 1 gm dose was administered in 94% of total joint arthroplasties with 64% (1105/1726) of these patients being underdosed. Furthermore, the authors found that weight-based dosing achieved higher levels of vancomycin at all points during surgery without increasing nephrotoxicity and acute kidney injury [10].

There are no studies comparing clinical or pharmacokinetic outcomes with different doses of clindamycin for surgical prophylaxis. Older pharmacokinetic studies show a good penetration of clindamycin into surgical tissues including bone [13–15]. Based on serum levels after intravenous administration, this suggests that commonly used doses of 600 mg or 900 mg should exceed the MIC of most relevant pathogens [1,15].

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QUESTION 3: Is one dose of preoperative antibiotic adequate for patients undergoing total joint arthroplasty (TJA)?

RECOMMENDATION: Despite the current guidelines from the Centers for Disease Control and Prevention (CDC) advocating for a single dose of perioperative antibiotics, these studies are underpowered and primarily in specialties outside orthopaedics. From the limited evidence available, it appears that a single perioperative dose of antibiotics, compared to multiple doses, does not increase the rate of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs). A randomized prospective study in patients undergoing elective arthroplasty is underway that should answer this question definitively.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 7%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Perioperative antibiotic prophylaxis remains an important strategy for minimizing one of the most devastating complications following TJAs, PJIs [1,2]. All current guidelines recommend the use of perioperative antibiotics [3–7] (Table 1). For arthroplasty, the costs and morbidities associated with PJIs have led to abundant research to reduce the rate of postoperative infections. To this end, perioperative antibiotics are widely used; however, hospital protocols vary from a single preoperative dose to several days of postoperative prophylaxis. Many surgeons administer antibiotics for a total of 24 hours as this is the maximum time period recommended by several current guidelines. However, there was a recent change in the guidelines provided by the World Health Organization (WHO) and CDC. They recommend against the administration of antibiotics in the postoperative period and that only a single preoperative antibiotic be administered, largely due to fears of increased bacterial resistance and side effects of unnecessarily prolonged antibiotics [4,5]. The 2017 CDC Guidelines issued this statement as a strong recommendation with high-quality evidence. However, the limited literature in arthroplasty cannot support this recommendation.

A recent systematic review and meta-analysis by Thornely et al. explored whether or not a single preoperative antibiotic dose is adequate for arthroplasty patients [8]. Their review returned four randomized controlled trials (RCTs) [9–12] with a total of 4,036 patients. In patients receiving postoperative prophylaxis, the infection rate was 3.1% (63/2055), compared to the rate (2.3%) of a single preoperative dose (45/1981). They concluded that postoperative antibiotics did not reduce the rates of infections; however, they reported that the quality of evidence was very low. Among the available RCTs, three include teicoplanin as a single dose treatment, which is currently unavailable in the United States [10,13,14]. Heydemann et al. randomized 211 patients to a single dose vs. 48 hours of nafcillin or cefazolin; no deep infections were seen in either cohort [9]. Ritter et al. compared a single preoperative dose of cefuroxime to 24 hours of postoperative prophylaxis in a small RCT of 196 patients, and found no postoperative infections in either group [11]. Lastly, Wymenga et al., in a multicenter RCT of 3,013 patients, compared a single preoperative dose of cefuroxime to a group receiving 3 total doses and found no significant differences in infections between groups. These

authors, however, recognize that their sample sizes were too small to detect a difference given the infrequency of PJIs and recommended continued use of postoperative prophylaxis until larger studies could be performed [12]. Other literature has been retrospective in nature, including reviews by Tang et al. [15] and van Kasteren et al. [16], each of which had < 2,000 patients and found no differences in infection rates between groups. The largest retrospective review by Engesaeter et al. showed a significantly higher revision rate with a single dose compared to four doses given on the day of surgery. The higher revision rate was partially caused by infections [17]. While the majority of studies are underpowered, a retrospective study by Tan et al. demonstrated no differences in 90-day or 1-year PJIs in the 4,523 patients that received a single dose of antibiotics compared to 16,159 patients that received 24 hours of antibiotics. Throughout all preoperative risk groups, however, patients with 24 hours of antibiotics demonstrated a trend toward a higher rate of acute renal failure.

It is important to recognize the different antibiotics used in each study noted above, as well as the small sample sizes. Furthermore, the meta-analysis performed by the CDC predominantly includes surgical interventions of the trunk without hardware retention (including vascular surgery, cardiothoracic surgery, general surgery, as well as ear, nose and throat). For surgeries of the extremity with retained implants, however, the evidence is more limited and consists of small RCTs or retrospective reviews without sufficient power to detect a statistical differences [13,14,18–25]. Among them, Gatell et al. did find a significant reduction in the rates of infections compared to a single preoperative dose for patients with retained metal implants [24]. These studies were also performed predominantly in the 1990s and early 2000s and modern antibiotics may have a different result. Given the devastating outcomes of PJIs for patients, we neither agree nor disagree with the CDC recommendations that antibiotics should not be provided postoperatively until sufficiently powered evidence can be provided through a multicenter RCT that is adequately powered and is considering the low event rate of infection in total joint arthroplasty. While future studies may show that there are no differences in single versus multiple doses of perioperative antibiotic prophylaxis, the current literature does not support this strong conclusion.

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TABLE 1. Guidelines for perioperative antibiotic prophylaxis

	Organization										
Recommendation from Guidelines	BOA 2012	AAOS 2014	SAOA 2016	ACS 2016	SCIP 2011	IHI 2012	ASHP 2013	SIGN 2014	WHO 2016	CDC 2017	NICE 2017
Appropriate antibiotic selection	√	√	√	√	√	√	√	√	√	√	√
Administration within 1 hr before surgical incision	√	√	√	√	√	√	√	√	√	√	√
Discontinuation after incision closure	–	–	–	No	–	–	–	–	√	√	–
Discontinuation within 24 h	Debatable	√	√	Unknown	√	√	Debatable	–	–	–	–

BOA, British Orthopaedic Association [1]; AAOS, American Academy of Orthopaedic Surgeons [2]; SAOA, South African Orthopaedic Association [3]; ACS, American College of Surgeons [4]; SCIP, Surgical Care Improvement Project [5]; IHI, Institute for Healthcare Improvement [6]; ASHP, American Society of Health-System Pharmacists [7]; SIGN, Scottish Intercollegiate Guidelines Network [8]; WHO, World Health Organization [9]; CDC, Centers for Disease Control and Prevention [10]; NICE, The National Institute for Health and Care Excellence [11]

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QUESTION 4: Should patients undergoing outpatient total joint arthroplasty (TJA) receive additional postoperative prophylactic antibiotics?

RECOMMENDATION: Despite the current guidelines from the Centers for Disease Control and Prevention (CDC) advocating for a single dose of perioperative antibiotics, the studies utilized to form these guidelines are underpowered and primarily in specialties outside orthopaedics. The limited evidence suggests that a single perioperative dose of antibiotics, compared to multiple doses, does not increase the rates of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs). A randomized prospective study in patients undergoing elective arthroplasty is underway, which should help answer this question definitively.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Administration of prophylactic antibiotics during TJA surgery has been demonstrated to be an important step in the prevention of SSIs and PJIs. During the early years of arthroplasty, prophylactic antibiotics for a few days postoperatively was routine. Over the last decade or so, there has been a movement towards reducing the amount of prophylactic antibiotics administered to TJA patients. Currently, antibiotics are administered to patients undergoing primary TJA for a period of 24 hours. The number of doses of antibiotics that need to be administered to TJA patients is not known.

In recent years, and with the increase in popularity of outpatient TJA, many patients undergoing primary TJA may only receive a single dose of antibiotics. It is not known if a single dose of antibiotics may predispose these patients to higher incidences of SSIs/PJIs. Recent guidelines for prevention of SSIs issued by the World Health Organization (WHO) and the CDC recommend against the administration of additional postoperative antibiotics [1–3]. The recommendation by these organizations is in an antibiotic stewardship practice intended to limit liberal use of antibiotics that can result in the emergence of antimicrobial resistance and also expose patients to adverse effects associated with administration of prolonged antibiotics [2,4,5]. Although the CDC Guidelines issued this statement as a strong recommendation with high quality evidence, there is limited literature in arthroplasty to support this recommendation.

A systematic review and meta-analysis by Thornley et al. has examined the issue of number of doses of antibiotic prophylaxis following TJA. The analyses revealed that the incidence of infections was 3.1% (63/2055) in patients receiving multiple doses of antibiotics compared to an infection rate of 2.3% (45/1981) in patients receiving a single dose of antibiotics [6]. They concluded that postoperative antibiotics did not have additional benefits in reducing the rate of infections. The authors of the systematic review did acknowledge that the quality of evidence related to this subject in TJA is low. Of the four available randomized controlled trials, three include teicoplanin which is currently unavailable in the United States [7–9]. Furthermore, studies are usually underpowered with one randomized trial enrolling only 196 patients when comparing a single dose of cefuroxime to 24 hours of prophylaxis [10]. In addition, Wymenga et al. compared a cohort of patients who received a single preoperative dose of cefuroxime to a cohort who received 3 total doses in 3,013 patients and found no significant differences in infections between the two groups [11]. However, the authors recognized that their sample size was too small to detect a difference given the infrequency of PJI and recommended continuing the use of postoperative prophylaxis until larger studies could be performed [11]. Additionally, in a national registry study, Engsaeseter et al. demonstrated higher revision rates in patients receiving a single dose of antibiotics compared to four doses given on the day of surgery [12].

Lastly, a retrospective study by Tan et al. demonstrated no difference in the 90-day or 1-year PJIs in 4,523 outpatient TJA patients that received a single dose of antibiotics compared to 16,159 patients that received 24 hours of antibiotics, regardless of the patient's preoperative risk of PJIs [13].

When comparing infection rates between outpatient and inpatient total joint arthroplasty, the majority of the literature demonstrates no difference in the rate of postoperative infection. In a large retrospective review of the PearlDiver Database, Arshi et al. found that patients who underwent outpatient TKA demonstrated an increased risk of prosthesis explantation (adjusted odds ratio (OR) 1.35, 95% confidence interval (CI): 1.07-1.72) as well as irrigation and debridement (adjusted OR 1.50, 95% CI: 1.29-1.77) compared to inpatients [14]. Despite these findings, multiple large national database studies have demonstrated no difference in postoperative infection between outpatient and inpatient TJAs [15–18].

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QUESTION 5: Does extended prophylactic antibiotics therapy for patients undergoing aseptic revision help reduce the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: In the absence of concrete evidence, we recommend the use of routine antibiotic prophylaxis (maximum 24 hours) for patients undergoing revision arthroplasty as long as the infection has been properly ruled out prior to surgery.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 81%, Disagree: 15%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Infections are a common cause of failures post aseptic revisions, occurring after 5 to 9% for total knee arthroplasties (TKAs), and 1.35 to 17.3% for total hip arthroplasties (THAs) [1–6]. One of the modalities used to prevent SSIs and/or PJIs after arthroplasty is administration of prophylactic antibiotic therapy [7–9]. Considering the high rate of SSIs and PJIs after revision arthroplasties, one can argue that extended prophylaxis for longer than 24 hours may be indicated in these types of surgeries. Several studies conducted in primary TKA and THA, indicate no difference in the rate of SSI in patients who received prophylaxis for 24 hours and in those who received it for longer than 24 hours [10–14].

A comprehensive literature search was performed to identify studies evaluating the potential role of extended antibiotic prophylactic therapy following aseptic revision arthroplasty. A single retrospective study conducted by Claret et al. on 341 patients undergoing revision arthroplasty was identified [15]. The authors compared the rate of PJI after changing their local protocol from administering teicoplanin and ceftazidim before surgical incision to doing so again two hours after as an antibiotic prophylaxis (2007–2010) prolonging this regimen until the fifth day after revision surgery (2010–2013). Several criteria concerning inflammatory markers, imaging and synovial fluid analysis were performed to

rule out infection prior to revision surgery. They observed that the PJI rate, occurring within three months after revision surgery, was lower in the long prophylaxis group compared to the short prophylaxis group (2.2% vs. 6.9%, p = 0.049). In addition, prolonged antibiotic prophylaxis was the only variable independently associated with a lower rate of PJI in their analysis (odds ratio (OR): 0.27, 95% confidence intervals (CI): 0.07–0.99). These data suggest that there might be a protective effect of prolonging antibiotic prophylaxis. However, although no other protocol modifications were made during the study period according to the authors, bias cannot be completely ruled out due to the retrospective nature of the study, especially as diagnostic methods to rule out an infection prior to revision surgery have been improved over recent years. Thus, there is a need for a randomized controlled trial that can examine this question. The PARITY trial, an international prospective randomized controlled trial currently conducted in the field of orthopaedic oncology, may provide us with additional evidence about the potential benefit of extended antibiotic prophylaxis in high-risk patients undergoing joint arthroplasty [16].

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QUESTION 6: Should duration and the type of antibiotic prophylaxis be altered in patients with a prior periprosthetic joint infection (PJI)?

RECOMMENDATION: Antibiotic prophylaxis should be tailored in patients with prior PJIs who are undergoing another subsequent elective primary or revision joint arthroplasty. Antibiotic prophylaxis should cover the initial causative organism(s) as well as the most common pathogens that can cause PJI with either single or dual antibiotics.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 6%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Patients with prior PJIs have a significantly higher risk for PJI in another prosthetic joint. Murray [1] described for the first time the risk of metachronous infections in multiple joints due to hematogenous spread. Studies by Parvizi et al. [2] and Leung et al. [3] both demonstrated that the majority of recurrent infections following PJI due to methicillin-resistant *Staphylococcus aureus* (MRSA) were reinfected with the same organism (66.7 and 89.9%, respectively).

Preexisting PJI was identified as a significant risk factor for a subsequent infection in a study by Luessenhop et al. in 1996 [4]. The presence of rheumatoid arthritis and a prior sepsis were shown to be significantly associated with a higher risk for development of subsequent PJI ($p < 0.001$ and $p < 0.0001$, respectively).

Another study by Jafari et al. [5] retrospectively identified 55 patients with PJI who had another prosthetic joint in place at the time of presentation. Eleven of them (20%) developed a PJI in a second joint, with the same bacteria in 36% of cases. Zmistowski et al. [6] found that recurrent PJI was due to the same organism as the index infection (PJI persistence) in 31.5% of 92 relapsed cases, following two-stage arthroplasty failure. A new organism (PJI reinfection) was observed in 68.5% of these cases. The only independent predictor of PJI persistence versus new infection was the original infecting organism, specifically Staphylococci (MRSA in particular). Moreover, polymicrobial PJIs were more frequently involved in immunocompromised hosts.

Bedair et al. [7] confirmed these observations in a multicenter, retrospective cohort study with 90 patients previously treated for PJI undergoing a second primary total hip or knee arthroplasty (THA or TKA). The study showed that patients with a history of PJI had a

higher risk of developing PJI in a subsequent THA or TKA (10 of 90, versus 0 of 90 in the control group; risk rato: 21.00; 95% confidence interval (CI), 1.25-353.08; p = 0.04). The authors found that a second PJI occurred more frequently in those whose initial infection was by a staphylococcal species (odds ratio (OR), 4.26 p = 0.04). The infecting organisms were the same species in the first and second PJI in 40% of cases, and all four of these were caused by Staphylococci.

Based on the available data, it appears that patients with a prior PJI who are undergoing elective arthroplasty are at higher risk of subsequent infection. The infecting organism for the second joint is most of the time same as the first infecting organism. Taken together, we feel that antibiotic prophylaxis for patients with a prior PJI who are undergoing an elective primary or revision arthroplasty needs to be altered. These patients may require administration of an alternative or additional antibiotic(s). For example, patients with a prior PJI by a gram-negative organism should receive prophylactic antibiotics against gram-negative bacteria. The same applies to patients with a prior MRSA infection and so on.

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QUESTION 7: Should prophylactic antibiotic therapy be administered for an extended duration in patients admitted to the Intensive Care Unit (ICU)?

RECOMMENDATION: Surgical prophylactic antibiotic therapy should not be administered for an extended duration in patients admitted to the ICU.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 82%, Disagree: 13%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The literature on surgical site infections (SSIs) classifies SSI risk factors into intrinsic (patient) related (e.g., age and underlying morbidity) and extrinsic (procedure) related (procedure, facility, pre-and intraoperative factors), both being either modifiable or not [1]. Admittance to the ICU is not treated as an independent risk factor, although risk factors for SSIs and risk factors for ICU admittance are correlated (age, co-morbidity, complexity of procedure). Using the published search algorithm from the World Health Organization (WHO) guideline's literature review and narrowing it with the term "ICU" and expanding it with the term "observational study," 180 articles were retrieved from October 1, 2015 until present (PubMed 39, Embase 84, Central 57). All abstracts were screened, but none found relevant for the question of extending antibiotic duration in patients admitted to the ICU. Using the unaltered WHO search algorithm (without narrowing with "ICU" and expanding with "observational study"), another 23 PubMed articles not covered within the first search were identified, but none of the screened abstracts were relevant. An unsystematic search in the PubMed Clinical Queries search was then performed with the terms "(Therapy/Broad [filter]) AND (antibiotic prophylaxis extended)" returning 245 articles. All titles were screened and abstracts of putative relevance reviewed and none were found to be relevant. The 34 articles retrieved with a modified search term (Therapy/Broad [filter]) AND (antibiotic prophylaxis prolonged ICU) were not found to be relevant either. Thus, no studies were found examining extended antibiotic prophylaxis in ICU patients when these patients are considered as a separate patient category and there are no data to support or refute an extended duration for preventing SSIs solely based on the admittance to the ICU.

However, ICU patients are included in the core randomized controlled trials (RCTs) showing no benefit of extending antibiotic prophylaxis past wound closure [2,3] albeit not specifically for arthroplasty patients. Since the publication of the Proceedings of the International Consensus Meeting on Periprosthetic Joint Infections in 2013, three major literature reviews and guidelines on prevention of SSI have been published from WHO [2], Centers for Disease Control and Preventiopn (CDC) [3], and the American College of Surgeons and Surgical Infection Society (ACS/SIS) [1], respectively. The CDC and WHO guidelines agree on not extending prophylaxis past wound closure based on a comprehensive systematic literature review, but the strength of the data supporting the recommendation for arthroplasty have been questioned [4–11]. The ACS/SIS makes an exception for prophylactic antibiotics past wound closure for joint arthroplasty, on the grounds that optimal antibiotic therapy for these patients remains unknown, but refers to the American Society of Health-System Pharmacists (ASHP); Infectious Diseases Society of America (IDSA); Surgical Infection Society (SIS); and the Society for Healthcare Epidemiology of America (SHEA) guidelines for a total antibiotic prophylaxis duration ≤ 24 hours [12]. A recently published meta-analysis and review on postoperative antibiotic prophylaxis in knee and hip arthroplasty did not find evidence to show efficacy of extended antibiotic prophylaxis for the prevention of SSI in patients undergoing total hip or knee arthro-

plasty. It did however question the quality of the existing evidence and call for new and sufficiently powered RCTs to settle the issue [12]. None of the guidelines or the extensive literature reviews underpinning them thus makes a distinction or specific recommendation for patients admitted to the ICU in general or for use of extended antibiotic prophylaxis for ICU patients in particular. However, ICU patients are included in the core RCTs forming the basis for the strong recommendations of not extending antibiotic prophylaxis after completion of the operation.

ICUs are heterogeneous and ICU capacity varies greatly across hospitals and countries. Consequently, both patient morbidity and hospital policies for ICU admittance will vary, making studies examining extended antibiotic prophylaxis based on ICU admittance unlikely. Should they be undertaken, their external validity would for the above-mentioned reasons be questionable.

The purpose of prophylactic antibiotic therapy in orthopaedic surgery is to prevent SSIs, for which a narrow-acting antibiotic with gram-positive coverage is a proven and sufficient option [13]. Prevention of remote infections in patients admitted to the ICU would have required a different prophylactic approach, including administration of broad-spectrum antibiotics and selective digestive decontamination (SDD), as opposed to the narrow spectrum antibiotics for SSI prevention. Although there are some data to support such a strategy, mainly from ICUs with low levels of antibiotic resistance [14], it remains highly controversial due to concerns of long- term resistance promotion and disturbance to the gut microbiome [15]. There is currently insufficient evidence to recommend its use in settings with high levels of antibiotic resistance [16]. Though an in-depth discussion of the issue is beyond the scope of the assigned question, the increased sense of urgency regarding resistance prevention following the 2014 WHO report on global resistance [17] speaks strongly against adoption of this strategy.

In addition to high awareness, prompt diagnostic workup and early initiations of broad empiric antibiotic therapy are the core interventions for reducing infection related complications in the ICU [18]. The continuation of a narrow-acting antibiotic therapy from the operating theater into the ICU may give a false sense of security and both obscure and delay these interventions, or even harm patients by promoting antimicrobial-resistant bacteria [19,20].

Arguably, the immunosuppressed state following surgery and trauma could be enhanced in patients ill enough to require treatment in the ICU, thus justifying implementation of antibiotic prophylaxis recommendation for immunosuppressed patients. However, despite not identifying studies addressing extended surgical antimicrobial prophylaxis (SAP) in arthroplasty for immunocompromised patients, the CDC guidelines give a strong recommendation (category 1a) against extended SAP in the immunocompromised patients based on their inclusion in the core RCTs with high quality evidence for SAP ≤ 24 hours postoperatively [21].

In an editorial commenting on a survey of 67 ICUs finding 50% of antibiotic prescriptions being continued beyond 72 hours despite absence of a definitive infectious source [22], the editor states that "there is a pervasive belief that an error of commission" (continuation of empiric antibiotics in the absence of evidence of infection) "is somehow better or safer than an error of omission" (ceasing antibiotic therapy when there is some chance–however slim–that the patient will benefit) [23]. This statement also applies fittingly to the question of extended prophylaxis in patients admitted to ICU; with a real threat of running out of effective antibiotics due to indiscriminate use, extending prophylaxis on the sole ground of ICU admittance should be avoided as there is neither theoretical rationale nor clinical evidence to support the practice.

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QUESTION 8: Does the use of allografts alter the recommended duration of prophylactic antibiotics?

RECOMMENDATION: No. Allografts are avascular materials that are prone to contamination and may serve as a scaffold for bacterial colonization and biofilm production, similar to a prosthesis or osteosynthetic material. However, it is difficult to establish a causal relationship between the use of an allograft and subsequent infection. Thus, there is no evidence to support the use of extended antibiotic prophylaxis.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 91%, Disagree: 6%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Allografts are typically utilized to address bone defects or damaged tendons at the time of revision procedures for patients who have already undergone multiple operations. By virtue of their operative history, these patients are already associated with a higher risk of infections (2 to 3 times) [1] compared to primary total joint arthroplasty patients. One recent study of fifty consecutive extensor mechanism allograft reconstructions in total knee arthroplasty (TKA) reported an infection rate of 10% [2]. The pooled infection rate from a systematic review and meta-analysis of proximal femoral allograft in revision total hip arthroplasty (THA) was reported to be 8% [3]. Allografts are avascular materials that, similar to a prosthesis or osteosynthetic material, are prone to contamination and may serve as a scaffold for bacterial colonization and biofilm production. However, it is difficult to establish a causal relationship between the use of an allograft and subsequent infection. The question of whether the antibiotic prophylaxis in such complex cases should be altered is a separate discussion from treating infections arising from undetected contamination of the allograft.

There are no high-quality studies available comparing differences between the duration of systemic antibiotic prophylaxis with and without allograft use in primary or revision total joint arthroplasty. Allograft bone may be utilized in different forms including untreated or processed, gamma-irradiated, chemically sterilized, and as fresh frozen product. A contamination rate of up to 23% immediately after aseptic procurement of unprocessed and unsterilized allograft has been reported [3]. Alternatively, sterilization reduces bacterial contamination rates approaching 0% after multiple decontamination processes [4]. An efficient "prophylaxis" may only be expected after using processed or sterilized allografts [5], perhaps by conferring additional local antimicrobial protection [6].

Two-stage procedures for infected TKA [7] and THA [8] with allograft bone demonstrated no differences with respect to short and long durations of antibiotic therapy and reinfection rates; however, antibiotic-impregnated bone cement was utilized in these cases. Withholding systemic antibiotic therapy has also been reported and recommended following revision (THA) for periprosthetic joint infection with adjunctive local antibiotic bone cement elution, except in cases of multiple-operated patients infected with highly-resistant organisms [9]. High quality studies evaluating the optimal duration of prophylactic antibiotics during allograft reconstructive procedures are warranted.

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1.4. PREVENTION: ANTIMICROBIALS (LOCAL)

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QUESTION 1: Is there sufficient evidence to support the use of antibiotic-loaded cement in primary total knee arthroplasty (TKA) or total hip arthroplasty (THA) to reduce the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: There is no conclusive evidence to demonstrate that routine use of antibiotic-loaded cement in primary TKA or THA reduces the risk of subsequent SSIs/PJIs. Recent high level evidence and registry data has not demonstrated a reduction in SSI/PJIs. Furthermore, the added cost, the potential for the emergence of resistant organisms and the potential adverse effect of antibiotics on the host provide adequate reasons to refrain from routine use of antibiotic loaded cement during primary total joint arthroplasty.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 38%, Disagree: 58%, Abstain: 4% (NO Consensus)

Authors: Yale Fillingham, Ali Parsa, Sergei Oshkukov, A. Seth Greenwald

QUESTION 2: Is there a role for the use of antibiotic-impregnated cement in primary total joint arthroplasty (TJA)?

RECOMMENDATION: Antibiotic-impregnated cement may be used during primary TJA to reduce the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs). The benefits of antibiotic-impregnated cement versus its cost and other potential adverse effects, may be most justified in patients at high risk of infection

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 7%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

The concept of using bone cement as a depot for antibiotics makes sense, as it allows for delivery of antibiotics directly to the site of potential infection. However, its role in the prevention of infection remains controversial [1–3].

The elution profile of cemented antibiotics has been evaluated, which demonstrates the elution kinetics of vancomycin, tobramycin, gentamicin, moxifloxacin and clindamycin are better than cefazolin, daptomycin, meropenem, ertapenem, cefotaxime, ampicillin, amoxicillin-clavulanate and cefepime [4–6]. Thus, the two most common antibiotics mixed with bone cement are vancomycin and aminoglycosides such as tobramycin and gentamicin.

Recent annual arthroplasty registries have shown that 96.3% of total knee arthroplasties (TKAs) and 93.7% of total hip arthroplasties (THAs) using cement, used antibiotic-loaded cement [7]. Plain cement has a slightly higher rate of revision than antibiotic-loaded cement when used in TKA [7]. Likewise, in THA, a lower rate of revision is observed for antibiotic-loaded cement in the first five years from surgery [7]. However, the rates of revision in THA were no different between antibiotic-loaded and plain cement beyond five years [7].

Commercially available antibiotic-loaded cements include Palacos® R+G (Zimmer Biomet), Simplex™ P with Tobramycin (Stryker), Smartset™ GHV (DePuy) or Refobacin® (BioMet), but several concerns remain about having readily available antibiotic-loaded cements. Studies have raised concerns regarding the following: (a) increasing microbial resistant; (b) insufficient dose of antibiotic in commercial preparations; (c) additional unnecessary cost; and (d) reduced mechanical properties of antibiotic-loaded cement [7–10].

While most primary THAs in the United States are done with cementless fixation [11], cemented THA is still commonly used in other geographic regions of the world. In the case of cemented arthroplasty, a retrospective comparison study on the use of antibiotic-loaded cement demonstrated an approximately 50% lower infection rate and lower rate of wound infection [11,12]. In addition to lower rates of infection, there is evidence that the addition of antibiotics to the cement leads to a reduction of all time failures of THA [13,14]. Results of a recent systematic review and meta-analysis on 12 clinical trials showed that conventional ventilation together with systemic antibiotics and antibiotic-loaded cement was most likely to provide the best protection against THA-related SSIs [15].

Previous evidence has shown that antibiotic-loaded cement together with systemic antibiotic prophylaxis was effective in reducing PJI in TKA compared with plain cement and systemic antibiotic prophylaxis [16–18]; however, new evidence does not support these results. Two recent prospective studies showed that antibiotic-loaded cement did not reduce the rate of deep infection following primary TKA compared with plain cement [19,20]. More recently, a systematic review on the use of antibiotic-loaded cement in total joint arthroplasty evaluated six articles encompassing 6,318 arthroplasties. Among the study population, 3,217 of these arthroplasties received antibiotic-loaded cement and 3,101 arthroplasties served as the control. Only two studies showed a significant effect of antibiotic-loaded cement in preventing deep infection in primary TKA. Contra-

dictory results were reported in the remaining four prospective and randomized clinical trial studies that showed no statistical difference between the two groups in terms of the incidence of deep or superficial SSIs [21]. In another meta-analysis, Kleppel et al. reported on 4,092 patients following TKA (3,903 primary TKA and 189 revision TKA). At the average follow-up time of 47.2 months for primary TKA, the use of antibiotic-loaded cement did not have a significant reduction in PJI/SSI [22]. Additionally, an analysis of 64,566 joints from the New Zealand Joint Registry demonstrated that the use of antibiotic-laden cement was actually associated with an increase in revision for PJI after a multivariate analysis (odds ratio (OR) 1.93, 95% confidence intervals (CI) 1.19 to 3.13) [23].

We must also consider the cost associated with the use of the antibiotic-loaded cement. Industrially manufactured antibiotic-loaded bone cement may be preferred, due to the ease of access [24]. However, biomechanical and elution testing has demonstrated 1-gram of vancomycin in handmade antibiotic-loaded cement can reduce the cost without compromising the mechanical strength or elution of the drug [25]. Additionally, vancomycin potentially has a higher antimicrobial activity when compared with gentamicin for methicillin-resistant *Staphylococcus aureus* (MRSA) while remaining heat-stable with adequate elution [26–28].

Overall, the literature still lacks an appropriately sized randomized clinical trial to better support the use of antibiotic-loaded cement.

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QUESTION 3: What is the optimal antibiotic(s) dosage to be used in cement during reimplantation that does not significantly interfere with the mechanical strength of cement used for fixation?

RECOMMENDATION: The mechanical strength of most cement is maintained if ≤5% (w/w) of antibiotics is added (equating to 2 grams in a 40 gram packet).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 3%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Several publications have investigated the mechanical characteristics of bone cement in vitro [1-12]. When reviewing in vitro studies on the mechanical strength of bone cement, one must assume that mechanical fixation strength in bone after a one- or two-stage revision for infection would equate to fixation of bone for a primary joint arthroplasty. The mechanical strength of antibiotic-loaded bone cement (ALBC) depends on the following: antibiotic dose, type of antibiotic, number of antibiotics, time of elution, method of mixing and incorporation of impurities/fat/blood [1-15]. Different types of cement also show a variable response to different doses of antibiotics [1, 4, 6, 9, 14].

Unfortunately, most investigations of one and two-stage exchange for prosthetic joint infections (PJIs) did not include details of antibiotic loading into reimplantation cement or used multiple different antibiotic loading regimens. Ultimately, 24 investigations with a consistent antibiotic loading of bone cement before prosthetic reimplantation during one- or two-stage revision for PJI were identified (Table 1). The collective information regarding the details of antibiotic loading in the reimplantation cement was compiled (Table 2).

Investigations examining the mechanical properties of ALBC are all in vitro investigations. Therefore, the loading conditions at the revision total hip and knee arthroplasty (THA, TKA) in vivo bone-implant interface are 1) poorly understood and 2) not adequately modeled to translate the mechanical behavior of ALBC from in vitro studies to these complex in vivo environments. In general, the addition of up to 2 gm of a single powdered antibiotic per 40 gm pack of polymethyl methacrylate (PMMA) has not been shown to have significant deleterious effects on ALBC mechanical properties [16]. More contemporary investigations quantifying the mechanical properties of dual-antibiotic loaded PMMA demonstrate that up to 3 gm total of powdered antibiotics can be included into a 40gm pack of PMMA before compressive strength is decreased below the International Organization for Standardization (ISO) standard [17].

Investigations in this literature review (Table 1) rarely addressed prosthetic aseptic failure following revision for PJI. Furthermore,

TABLE 1. Summary of literature pertaining to antibiotic-loaded cement

PubMed ID	One-stage vs. Two-stage	# Investigated Prostheses	Follow-up Interval (months)	ALBC Details	% Failure
24923669 [18]	One	28	78	1 gm Gent, 1 gm Vanc per pack	0
7497685 [19]	Two	26	31	1.2 gm Tobra per pack PMMA	0
10535593 [20]	Two	40	40	1.2 gm Tobra per pack	25
10990301 [21]	Two	45	48	1.2 gm Tobra per pack	9
11097443 [22]	Two	69	63	1 gm Tobra per pack	9
11216723 [23]	Two	53	56	1.2 gm Tobra per pack	17
12051001 [24]	Two	10	18	0.5 gm Gent per pack	0
15343539 [25]	Two	24	33	2.4 gm Tobra, 1 gm Vanc per pack	8
15991126 [26]	Two	44	65	1.2 gm Tobra per pack	3
15662313 [27]	Two	50	73	1.2 gm Tobra per pack	4
17162176 [28]	Two	21	52	1 gm Tobra per pack	5
17966006 [29]	Two	24	48	1 gm Gent, 1 gm Clinda per pack	4
19553076 [30]	Two	53	49	750mg cefuroxime	17
19299221 [31]	Two	13	48	2 gm Vanc per pack	0
20087702 [32]	Two	27	58	1 gm Gent, 1 gm Clinda per pack	4
20202852 [33]	Two	10	31	0.5 gm Gent, 1 gm Vanc per pack	0
22863338 [34]	Two	21	32	0.5 gm Gent, 1 gm Vanc per pack	4
26272061 [35]	Two	82	36	0.5 gm Gent per pack	15
21866421 [36]	Two	117	46	1.2 gm tobra,1 gm Vanc per pack	28
14563794 [37]	Two	58	41	0.6 gm Tobra per pack	4
15190550 [38]	One	22	120	1.2 gm Tobra per pack	9
10611868 [39]	One	24	108	2 gm 1st Generation Cephalosporin per pack	8.3
721853 [40]	One & Two	67	24	0.5 gm Gent per pack	12
3769248 [41]	One	100	38	0.5 gm Gent per pack	9

TABLE 2. Summary of pooled data pertaining to antibiotic-loaded cement at reimplantation

Variable	Tobra (T)	Gent (G)	Vanco (V)	Cefuroxime	1st Gen cephalosporin	V+T	V+G	G+Clinda (C)
Number of studies	10	4	1	1	1	2	3	2
Two-stage	9	3*	1	1	-	2	2	2
One-stage	1	2*	-	-	1	-	1	-
Dose per 40 gm PMMA pack	0.6-1.2 gm	0.5 gm	2.0 gm	750mg	2.0 gm	1.0 gm V 1.2-2.4 gm T	1.0 gm V 0.5-1.0 gm G	1.0 gm G 1.0 gm C
Number of prostheses	428	259	13	53	24	141	59	51
Average follow-up (mo)	59	29	48	49	108	40	47	53
PJI recurrence incidence (%): range and average	0-25 8.5	0-15 9	0 0	17 17	8 8	8-28 18**	0-4 1.3	4 4

* Numbers do not add up due to one study containing both one-stage and two-stage procedures
** Average significantly skewed to lower value as one study with 28% PJI recurrence incidence included 117 of the total 141 patients

reports of aseptic prosthetic loosening in the setting of prior revision THA or TKA for PJI must be cautiously interpreted as it may represent PJI recurrence. Therefore, conclusions cannot be drawn regarding the clinical effectiveness of any specific ALBC formulation in the prevention of aseptic THA or TKA loosening following revision for PJI.

At this time, there is no definitive conclusion on what prosthetic reimplantation ALBC formulation provides the best eradication of PJI and/or is most protective against subsequent prosthetic aseptic loosening. Any inferences made as a result of this review must be cautiously adopted into clinical practice due to the multiple confounding variables present in different PJI treatment investigations (e.g., patient characteristics, organism resistance profiles, antibiotic spacer differences, length of antibiotic treatment before and after prosthetic re-implantation, etc.). This review demonstrates that prosthetic reimplantation bone cement can be loaded with a wide range of single or dual antibiotics and provide successful PJI control following one- or two-stage PJI revision surgery in a high percentage of prostheses. However, when only ALBC regimens supported by more than one study and 50 patients are considered, prosthetic re-implantation using ALBC containing either 1 gm vancomycin and 0.5-1 gm gentamicin per 40 gm pack of PMMA or 1 gm clindamycin and 1 gm gentamicin per 40 gm pack of PMMA appear to have the optimal ability to control PJI while not resulting in mechanical compromise of the PMMA.

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1.5. PREVENTION: OPERATING ROOM ENVIRONMENT

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QUESTION 1: Does performing a primary total joint arthroplasty (TJA) after a dirty case (infection or open abdomen) in the same operating room increase the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: The little data on this subject suggests that the risk of PJIs may be higher when an elective arthroplasty follows a contaminated case. The risk may be reduced if terminal cleaning of the operating room can be done after the dirty case. Further studies are necessary to elucidate this connection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 4%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

A comprehensive literature review was performed in order to identify all studies on the effect of infection risks in primary TJA following a contaminated case. Searches for the terms "total joint arthroplasty," "infection risk," and "infected case" with different Boolean operators were performed using the search engines Medline, Embase and Cochrane that were searched through February 2018. Inclusion criteria for our systematic review were all English studies (Level I-IV evidence) that reported on infection risk for primary TJA following a contaminated case. Exclusion criteria were non-English language articles, studies > 10 years old, nonhuman studies, retracted papers, case reports, review papers, studies with less than <10 patients in the sample size, studies without clinical follow-up/infection rates and technique papers without patient data. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria were followed. The initial search resulted in 921 papers. After removal of duplicates and evaluation of titles, 170 titles were evaluated, 24 full text papers were read and 4 studies met full inclusion and exclusion criteria to allow for analysis.

There is limited data in literature specific to infection risk when performing primary TJA after a contaminated case, as the number of studies is limited and the number of TJAs performed after an infected case is also restricted. A systematic review was performed specifically evaluating whether nosocomial pathogens persist on inanimate surfaces, such as pathogens from infected surgical cases remaining on surfaces in the operating room [1]. Almost all pathogens including respiratory and gastrointestinal viruses persisted for days on inanimate surfaces, with many gram-positive, gram-negative and fungal pathogens remaining for months. However, pathogen persistence was disrupted if preventative surface disinfection was performed and this was corroborated in a study of 31,499 TJAs where terminal cleaning was effective at reducing bioburden after an infected case and did not increase the likelihood of infection when a case was performed the next day [2]. On the other hand, this same study also demonstrated that infection risk increased by 2.4 times if a TJA case followed an infected case in the same room on the same operative day. Another study

demonstrated this similar finding, as one patient of 39 TJA patients (2.6%) developed an infection after a contaminated case and the organism *Cutibacterium acnes* was the same as the one isolated from the previous infected case [3]. Of note, the sample size was small in this study, although this study encompassed a 5-year study period, indicating that few TJAs were performed after infected cases. On the other hand, a previous study examining 85 TJAs performed immediately after an infected case demonstrated no difference in deep or superficial infection risk at 12 months when compared to a matched cohort of 354 TJAs that did not follow a contaminated case [4]. The pathogen from the TJA infection that followed a contaminated case was due to a different organism than the pathogen present in the preceding infected case. Further research is needed to determine whether infection risk is increased when a primary TJA is performed after a contaminated surgical case.

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QUESTION 2: Does the use of sterile surgical vests decrease the risk of contamination or incidence of infection following total joint arthroplasty (TJA)?

RECOMMENDATION: The use of sterile surgical vests has no bearing on the incidence of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) following orthopaedic procedures.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 85%, Disagree: 6%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

The optimal choice of gown material, type of surgical attire and method of donning operating room personal protective equipment has long been debated. Despite the current era of evidence-based medicine, surgical clothing remains steeped in historic practices based on literature over 30 years old and the notion of "what we have always done." Overall, the evidence surrounding surgical gowning/vests is poor. On systematic review, using PubMed, Ovid-MEDLINE®, Embase, PEDro, Cochrane Library, Scopus, Web of Science, ERIC and CINAHL Plus, we identified 1,356 articles using search terms related to surgical vests, gowns or suits; orthopaedic vests, gowns, suits, exhaust, helmet and surgical textiles. Of these, only 25 were pertinent to our study and represented a heterogeneous group.

It is an issue of significant socioeconomic value given the risk of exposure to contaminants and SSI following TJA. Guidelines from various bodies (World Health Organization, Association of Perioperative Registered Nurses, National Institute for Health and Care Excellence) appear to be based more in "expert opinion" and pragmatic approach rather than scientific evidence. On occasion, these guidelines appear contradictory and incomplete [1,2]. Many papers had major methodological flaws in study design and severe observer bias such that they would not merit inclusion in the study. Of those studies included, several use unproven links such as the reduction of bacterial counts and skin squamous cells as a proxy for infection.

The part of the surgical gown below the level of the operating table and above the chest level appears to be more contaminated [3]. Gowning and gloving appear to generate air particles in an operating room environment, although this appears less so at the level of the operating table under laminar airflow [4].

Exhaust suits have been thought to contribute to reduction of SSI for many years [5]. In addition, it is advocated that they protect the surgical team from contamination during orthopaedic procedures [6]. In a randomly allocated study of different surgical attires used for total knee arthroplasty, body exhaust suits produced less air contamination than occlusive polyester gowns, but no difference was identified in wound contamination [7]. In a combination of hip and knee arthroplasty series, filtered exhaust helmets provided no increased protection against bacterial contamination in the area of the surgical field versus conventional hoods and masks [8]. In comparison to established occlusive polyester gowns, more modern liquid-proof fabric gowns have received criticism that they produce increased air contamination [9]. Disposable non-sterile hoods appear to be equally efficient to helmet systems in containing bacteria in air and surgical site surface [10]. In another study, space suits appear to cause more particle counts in the operating room with surgeon motion compared to standard surgical gowns [11]. Space suits do seem to offer protection in bacterial air contamination at the surgical site compared to conventional surgical suits [12]. Disposable polypropylene clean air suits with cuffs at the sleeves and legs appear to reduce air contamination compared to other suits [13,14]. Reusable surgical gowns show more bacterial penetration compared to disposable spun-bonded gowns [15,16]. Tightly woven special scrub suits do not seem to reduce air or wound contamination with methicillin-resistant *Staphylococcus epidermidis* (MRSE) and the most common source of MRSE remains the patient [17].

Modern positive-pressure surgical helmet systems differ from the earlier negative-pressure body exhaust systems, which were noted to reduce surgical site infection [18]. Furthermore, not all surgical helmet systems compare similarly as far as the contamination of the glove-gown interface is concerned. Specifically, positive pressure systems show more contamination in this area, even compared to conventional sterile gowns [19]. This has been attributed to contamination at the glove-gown interface [20,21]. A randomized study of standard surgical gowns and positive-pressure surgical helmet systems, with and without cuff/glove taping, found

more positive surgical site cultures with helmets and tape, but this was not statistically significant [22]. Direct contact with the sterile helmet is discouraged as a significant number may be contaminated during joint arthroplasty and sterility should not be presumed [11]. In a very large cohort of primary total hip arthroplasty, procedures where a body exhaust system was used showed a higher deep infection incidence, but this did not prove to be a risk factor in multivariate analysis [23].

Overall, the study quality on the subject of sterile surgical attire is low in most instances. Tangible conclusions on which type of attire, material, system and combinations leads to reduction of contamination or incidence of infection following TJA cannot be reached. There appear to be several reports of contamination using sterile helmet systems. Whether that leads to increased incidence of infection remains to be shown. In summary, a weak recommendation of sterile surgical gowns for TJA is put forward, as best "common sense" practice in the absence of robust evidence [24], but the use of modern helmet systems would not be recommended in preventing SSI.

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QUESTION 3: Does the use of personal protection suits (space suits) influence the rate of surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing joint arthroplasty?

RECOMMENDATION: In the absence of strong evidence, we believe the use of personal protection suits does not reduce the rate of subsequent SSIs/PJIs in patients undergoing joint arthroplasty.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 87%, Disagree: 11%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Initial personal protection suits, which aimed to protect the surgical site by reducing microbial contamination and subsequent infection from the operation staff, were negative pressure body exhaust suits with inflow and outflow tubing creating a negative pressure inside the suit. Shed particles were vented away from the surgical site by the tubing. Due to the cumbersome nature of the tubing, more port-

able surgical helmet systems were developed. These helmet systems typically have an intake fan on the helmet, allowing the air to flow across the person's head and neck, and are exhausted by openings in the gown, usually through the lower portion of the gown or other potential openings.

A systematic review of helmet systems and body exhaust suits was published in 2016 [1]. Helmet systems or body exhaust suits were compared to conventional gowns for outcomes of (i) air contamination, (ii) wound contamination and (iii) deep infection. Sixteen articles met inclusion criteria for the various outcomes.

Air contamination: Four studies compared helmet systems to conventional gowns [2–5]. One study [4] reported reduced air contamination; the other three showed no difference [2,4,5]. Five [6–10] of seven studies comparing body exhaust suits showed reduced air contamination. Two studies showed no difference in air contamination compared to conventional gowns [11].

Wound contamination: A single study showed no statistical difference in wound contamination comparing helmet system to conventional gowns [4]. Two of four body exhaust suit comparison studies found a significant advantage to body exhaust suits with less wound contamination compared to conventional gowns [12,13]. The other two studies trended in favor of body exhaust suits [6,7].

Deep infection: Three registry data studies, reporting on four series of patients (two series of total hip arthroplasty (THA) and two series of total knee arthroplasty (TKA) patients), totaling just over 175,000 patients, compared helmet systems to conventional gowns and used reoperation for infection at 6 months [14] or one year as the outcome [15,16]. Hooper reported a statistically higher rate of reoperation for infection within the first six months when helmet systems were used: THA - 0.19% with helmet system vs. 0.06% conventional gown, $p < 0.0001$, and TKA - 0.24% with helmet system vs. 0.098% conventional, $p < 0.001$ [7]. Namba et al. showed no difference in reoperations for infection at one year when a multivariate analysis was used for both THA and TKA [8,9]. Pooled data from these four series showed a non-statistically significant ($p = 0.09$) increase in deep infections (risk ratio (RR) 1.67, 95% confidence interval (CI) 0.92, 3.05) [17].

In contrast, the four studies involving 3,990 patients comparing body exhaust suits to conventional gowns showed a decrease in deep infection when body exhaust suits were used [6–8,13]. The deep infection rate at mean 2.5 years follow-up was 0.17% (3 of 1,795) in the body exhaust group and 1.0% (16 of 1,604) in the conventional clothing group ($p < 0.01$). When data from the above studies was combined in a fixed meta-analysis model, body exhaust suits were associated with a significant reduction in deep infection rates (RR 0.11, 95% CI 0.09-0.46).

Following the publication of the helmet system systemic review, two additional New Zealand Joint Registry data studies have further analyzed the impact of surgical helmet systems on reoperation for infection at 6 and 12 months [18,19]. Multivariate analysis showed no statistical increase (or decrease) in reoperation for infection when surgical helmet systems were used for both primary hip and knee arthroplasty. In the primary knee study there was a non-statistically significant trend ($p = 0.052$) towards reoperation for infection at six months when surgical helmet systems were used (odds ratio (OR) 1.53, 95% CI 1.00 to 2.34) [18]. One additional study, comparing a helmet system to a conventional gown in a simulated surgical environment enclosure, used particle and microbiological emissions as the outcome. Particle counts were statistically higher, while microbiological emissions trended (but not significantly) higher in the helmet system experiments [17].

It is important to note that the type of helmet systems and gowns used were not reported in the above studies on deep infection. Helmet systems vary with respect to the fan type, fan speed, location of exhaust from the gown and material of the gown/toga used with the helmet system. These variables may also influence the potential for contamination. In a study by Fraser et al. one helmet/toga system showed significantly higher rates of contamination at the gown-glove interface relative to other helmet systems and a conventional gown [3]. The other helmet systems in that study showed no statistically increased rate of contamination compared to a conventional gown. The helmet system with the higher risk of contamination at the gown-glove interface used a toga with sleeves made of a stiffer, plasticized material that likely allowed for greater egress of particles at the gown-glove interface.

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QUESTION 4: Does changing the drapes during debridement, antibiotics and implant retention (DAIR) affect the rate of success?

RECOMMENDATION: The impact and effectiveness of changing the drapes during DAIR has not been investigated and therefore it can be performed at the surgeon's discretion.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 94%, Disagree: 5%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

DAIR is a viable and effective option for the management of acute periprosthetic joint infections (PJIs) [1,2]. Published success rates for patients responding to DAIR treatment range from 14 to 100% [3,4]. However, as stated by Tsang et al., published rates improved after 2004 with a pooled mean proportion of success of about 72% [3]. The reason for improvement of success of DAIR is certainly multifactorial and includes a better understanding of the importance of performing a thorough debridement. Numerous factors that influence the outcome of DAIR have been identified including the timing of surgery, the number of procedures, the responsible microorganism, the duration of antibiotic treatment, the exchange of removable components and other factors [3,5–9].

In a review article on DAIR treatment, the only statistically significant determinants of outcome were an early timing of debridement (with a median of < 7 days from the onset of symptoms of infection) and the exchange of removable components [3].

Even though some papers consider the question [10], there are no studies that assess the impact of changing the drapes during DAIR. After a systematic review of 51 papers, only one study was identified that mentioned the use of clean draping during the surgical procedure [11]. Other studies on one-stage exchange after PJI also mention redraping after implant removal and completion of debridement [12].

Changing the drapes during DAIR can be performed at the surgeon's discretion. Further studies are needed to investigate their role and effectiveness in the treatment of early PJI.

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QUESTION 5: Does the use of separate instruments for each side reduce the rate of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing simultaneous bilateral total hip or knee arthroplasties (BTHA or BTKA)?

RECOMMENDATION: No. The use of separate instruments for each side does not appear to reduce the rate of subsequent SSIs/PJIs in patients undergoing simultaneous BTHA or BTKA.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 72%, Disagree: 19%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

The proportion of one-stage bilateral total joint arthroplasty (BTJA) to unilateral total joint arthroplasty is increasing in the United States. This trend may be driven by the epidemic of obesity and its contribution in the progression of osteoarthritis and the expansion of total joint arthroplasty (TJA) to younger, healthier and more active patients [1–3]. All of these factors result in a higher demand for the procedure. Advances in anesthesia, surgical technique and perioperative care may further contribute to the increase of one-stage BTJA [4].

One-stage BTJA is a relatively safe procedure, especially following appropriate patient selection [5,6]. The benefits of one-stage BTHA include a single anesthesia and single hospital stay, resulting in cost reduction [7] and shorter overall hospital length of stay (LOS) [8,9]. Some studies advocate BTHA as they have demonstrated that rates of perioperative complications are similar between one-stage BTHA and unilateral total hip arthroplasty (THA) [10,11]. On the other hand, opposing studies have found that one-stage BTHA poses greater risks to patients, including increased transfusions, greater adverse events and suboptimal functional outcomes [12–15]. Most studies focus on mortality, pulmonary embolism (PE), deep venous thrombosis (DVT) and cardiovascular complications, but data on SSIs or PJIs is limited in the literature.

SSI/PJI is a significant problem and is associated with increased morbidity, mortality and medical expenditures [16–22]. Increased surgical duration, blood loss and need for allogeneic blood transfusion are risk factors for SSI/PJI [23,24]. The literature is divided with respect to wound infection rates following one-stage BTKA and unilateral total knee arthroplasty (TKA). Authors who have observed a higher infection rate in one-stage BTKA surgery blame the longer operative times, increased number of medical personnel in the operating room and a lack of rescrubbing, redraping and instrument changes for the second arthroplasty [25]. Others have reported rates of SSIs after one-stage BTKA and BTHA to be no higher than those following procedures performed unilaterally or staged. This may be due, in part, to the younger, healthier patient population selected for these procedures [26,27].

A potential source of SSI unique to one-stage BTJA is the use of the same set of instruments in both joints. The procedures may be completed using one or two surgical teams, as well as one or two sets of instruments. Reduced SSI/PJI following BTJAs using separate instruments for each side has not been demonstrated. There is currently limited and inconclusive evidence in the literature [28–31].

In 2006, Gonzalez Della Valle et al. [28] considered the hypothesis that the prevalence of early deep infection would be lower on the second side when a completely new set of sterile instruments was used for the second side. The authors retrospectively reviewed the prevalence of deep infection in 271 consecutive cases using two different sterile setups (group 1) and 289 cases using the same setup (group 2). In group 1, there was one deep infection affecting the first side, while there were no deep infections in group 2. In group 2, one patient developed a superficial infection on the second side requiring readmission and intravenous antibiotics. Given the very low prevalence of deep infection of the first and second side (0.2% and 0%, respectively), the study was underpowered to detect a difference – 2,300 patients would be needed in each group to achieve statistical significance. The results of this study should be considered with caution, as they are the result of experienced surgical teams specialized in hip arthroplasty surgery, operating in laminar flow rooms, and using body exhaust suits. Without these conditions, the rate of infection in single-stage bilateral hip arthroplasties performed with the same set of instruments may be higher. Based on this experience, the use of the same set of instruments for the second side in the operating conditions described in this study appears to be safe [28].

The remaining three studies compared outcomes of bilateral to unilateral TKAs. Two of the three studies used separate instrument sets in the bilateral procedures and observed infection rates of 0% in 227 patients [29] and 2.7% in 92 patients [30]. The final study used the same set of instruments in the bilateral procedures and observed an infection rate of 3.5% in 72 patients, attributing possible sources of infection to prolonged operation time, increased number of assistants in the operating room, not redraping and rescrubbing and not changing instruments [31]. The latter conflicts with the conclusion reached by Gonzalez Della Valle et al. which posited that use of the same instruments is considered safe [28]. Three of the four studies found one-stage BTJA to be generally safe [28–30], with the exception of Luscombe et al. [31] who concluded that staged bilateral procedures may be safer.

There is currently not enough clinical evidence to show that the use of separate instruments for each side during simultaneous BTJA reduces the rate of subsequent SSI/PJI. While the retrospective study from Gonzalez Della Valle et al. did find no difference in infection rates between same and separate instrument procedures, its retrospective nature and lack of statistical power are not strong enough to reach a clinical conclusion regarding standard of practice for using one or two instruments sets. The use of one instrument set does appear to be safe with the available evidence.

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QUESTION 6: Does routine use of a new set of surgical instruments and equipment following debridement and before reimplantation reduce the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs) recurrences? Is it necessary to change all surgical fields before the final reimplantation in septic revision surgery?

RECOMMENDATION: The change of the surgical field following debridement of an infected joint leads to a reduction in the bioburden and stands to improve outcome of surgical intervention and should be considered.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 7%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

There are no specific studies that have addressed the levels of contamination of instruments in infected revision surgeries. Different studies have addressed surgical instrument contamination in orthopaedics and other specialties with no definite recommendations. Some have shown a level of surgical instrument contamination in contaminated and infected operations, implying the instruments will be contaminated by the surgery itself [1,2]. Furthermore, studies have shown that instruments also become contaminated during what are considered to be clean procedures [3].

Pinto et al. showed that in clean orthopaedic surgeries, 47% of the instruments were contaminated. In the same study, an even higher rate of 70% had positive cultures in contaminated surgeries and up to 80% in infected cases [4]. They concluded that there was a significant difference in microbial growth between the clean and contaminated surgeries and between the clean and infected surgeries. In a different study, Evangelista dos Santos et al. evaluated patients undergoing gastrointestinal surgery and found that the surgical wound classification significantly affected the microbial load recovered on instruments [5]. Microbial loads were higher on instruments used for contaminated procedures.

Not all studies share the same results. There is a contradictory report from Nystrom which found that regardless of the classification of orthopaedic operations as clean, contaminated or infected, similar contamination rates were observed in splash basins (75%, 80% and 71% respectively) [6]. They concluded that the data did demonstrate a relatively higher correlation between splash basin contamination and contaminated and infected cases but this was not significant.

When evaluating correlation between contaminated instruments and infection risk, only one study was identified. Dancera et al. showed post sterilization contamination of surgical instruments was linked with an increased rate of deep SSIs in orthopaedic and ophthalmological patients [2]. This seems to link contamination of surgical instruments to increased risk of infection.

In joint arthroplasty surgery literature, Davis et al. showed that in 100 consecutive primary hip and knee arthroplasty operations under laminar flow, instruments get contaminated. 11.4% of suction tips, 14.5% of light handles, 9.4% of skin blades and 3.2% of deep blades were seen to have positive cultures [7]. In conclusion, 63% of operations showed contamination in the field of operation. In a different study evaluating electrocautery tips, Shahi et al. found in 100 consecutive primary total hip arthroplasties (THAs) and aseptic revision THAs that up to 6% of tips were contaminated [3]. None of these patients continued to have a PJI/SSI. Robinson et al. also found that 41% of suction tips had evidence of bacterial colonization in THA surgery undertaken in ultraclean air operating rooms [8]. Furthermore, few studies have focused on elements of the surgical field other than the instruments. Beldame et al. found a surgical

glove perforation rate of 3.5% and glove contamination rate of 6% during total hip reduction (THR) and an overall glove contamination rate of 3.38% in elective THA [9].

Literature suggests that instrument contamination even occurs during primary and clean arthroplasty surgery. This contamination does not seem to translate into an increased risk of SSI/PJI. Although some studies do show that contamination is higher in contaminated and infected surgeries, conflicting evidence exists in whether it translates into clinical infection. Non-arthroplasty literature seems to support that contaminated instruments translate to active infection but few low evidence studies have been identified.

We consider that with these findings, although limited evidence is available, especially related to infected arthroplasty surgery, the routine use of a new set of surgical instruments and equipment following debridement and before reimplantation in infected revision arthroplasty surgery should be considered. This could potentially reduce the risk of having contaminated instruments and therefore reduce the risk of contamination overall in the surgical field, potentially reducing the risk of SSI/PJI.

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QUESTION 7: Is there a concern for contamination of the surgical field by particles, such as cement, that may escape the wound intraoperatively by coming into contact with the ceiling light or facial masks and fall back into the wound?

RECOMMENDATION: There is logically a high risk that particles which fall into the wound after coming into contact with unsterile equipment (e.g., ceiling lights, facial masks) will contaminate the surgical field. However, no studies investigating this hypothesis directly exist in the current literature. We recommend that surgeons must be conscious of, and take precautions, in order to prevent particles from falling into the surgical field, and should such a scenario arise, to use copious antiseptic solutions, such as dilute betadine, in order to irrigate the wound.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 97%, Disagree: 2%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Several studies have shown that high-speed cutters in primary hip arthroplasty and spinal surgery can produce aerosols [1–3]. These aerosols, possibly contaminated with bacterial, fungal or viral agents, are spread over the operating room (OR) and contaminate the environment and all personnel present during the surgical procedure. In revision hip or knee arthroplasty, different tools and high-speed cutters are used for removal of cement from the bony cavities. Some of these tools, particularly ultrasound devices, can vibrate at a high frequency leading to a dissemination of cement particles throughout the operating room [4,5]. In some instances, other instruments such as chisels and osteotomes, used for cement extraction, can propel particles into the ceiling, OR lights or body parts of surgeons or assistants participating in the surgery. The particles that come in contact with an unsterile surface such as the ceiling, facial mask or lights, have the potential to fall back into the wound thereby acting as a vehicle for the transport of infectious organisms into this sterile area.

There are no studies in the literature evaluating the effect of debris that come in contact with an unsterile surface and fall back into the wound. Any assumptions must therefore be based on literature highlighting the role of airborne particles in the OR and their correlation with the risk of surgical site injection/periprosthesic joint infection (SSI/PJI). Airborne particles are a source of bacterial inoculation of the wound and can result in postoperative SSI/PJI [6–8]. Therefore, significant efforts are made to reduce the airborne particulate load. Studies suggest that particles larger than 10µm are large enough to carry viable bacteria [9]. Furthermore, as studies suggest that air turbulence and shedding of bacteria by OR traffic can result in an increase in bacterial counts in the sterile fields [10–12], it may be plausible to assume that larger debris may cause similar disruptions in airflow and increase the bioburden. Additionally, existing literature suggests that splash basins used in the OR are often contaminated with bacteria [13,14]. Non-sterile wound debris falling into such basins may be contributing to their contamination, but no study has demonstrated this theoretical possibility.

In summary, despite the absence of any specific studies demonstrating a contamination risk of the sterile operating field from "splash-back" of wound debris, we recommend that surgeons make every effort to mitigate this problem. Rachha et al. reported a technique for cement extraction that will likely prevent this problem. This was a transparent pulsed lavage shield made with plastic material that does not hinder the dexterity or vision of the surgeon. Non-

sterile objects, such as the OR lights, should be kept as far away from the surgical field and sterile equipment as practically possible. It is plausible that contaminated particles may fall into the surgical field during orthopaedic procedures, if such scenario arises, we recommend that copious irrigation of the operative field with the use of normal saline and antiseptic solutions, such as dilute betadine, be performed.

Further basic science (simulation-based) and implementation research in this area is warranted.

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1.6. PREVENTION: SURGICAL TECHNIQUE

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QUESTION 1: Does the use of a tourniquet influence the rates of surgical site infections/periprosthetic joint infections (SSIs/PJIs) in primary or revision total knee arthroplasty (TKA)?

RECOMMENDATION: The literature is inconclusive regarding the use of a tourniquet during TKA and its potential to increase the risks for SSIs/PJIs in TKAs. Tourniquet times and pressures should be minimized to reduce this risk.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 89%, Disagree: 9%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

The use of a pneumatic tourniquet during TKA has long been a standard for this procedure. However, concerns have arisen over the ischemic injury that can occur from tourniquet use. This has prompted many authors to conduct studies evaluating the use and non-use of a tourniquet and its effect on perioperative blood loss, postoperative pain and function and postoperative complications [1–7]. However, many of these studies are small, randomized controlled trials (RCTs) that lack the power to definitively state the influence om tourniquet use of SSIs and PJIs.

Liu et al. showed in a RCT of 52 patients undergoing simultaneous bilateral TKA that tourniquet use was associated with greater wound ooze and blistering, as well as the only deep infection in the cohort occurring in a TKA case that had been performed while using a tourniquet [8]. In a 31-patient RCT, Clarke et al. demonstrated that increased tourniquet pressures led to sustained wound hypoxia up to one week following surgery [9]. A meta-analysis by Yi et al. evaluated 13 RCTs of tourniquet use comprising 859 patients. Of these 13 studies, 3 evaluated infection risk, SSI and PJI together, and they found that tourniquet use was significantly associated with an increased risk of infection [6]. A meta-analysis by Zhang et al. found a similar pooled result with tourniquet use associated with a greater risk of non-thrombotic complications, infection included [10].

Longer tourniquet times, and by virtue longer surgical times, have been associated with an increased risk for both SSI and PJI [11–13]. Willis-Owen et al. in a series of 3,449 consecutive TKAs found that patients who went on to have a SSI/PJI had significantly longer tourniquet times than noninfected patients [11]. Ricciardi et al. found a similar result in their analysis of perioperative variables affecting 30-day readmission [12]. Na et al. evaluated early release of the tourniquet following cementation of components versus reinflation of the tourniquet after controlling bleeding in 206 patients and found that the increased tourniquet time for patients in the reinflation group did not affect the rate of wound complications, SSI or PJI [14]. However, none of these studies were able to propose a cutoff for tourniquet time over which the risk of SSI and PJI begins to increase. These studies also did not differentiate between operative time and tourniquet time. As increased surgical time is a known risk factor for

SSI and PJI, the confounding effect of increased surgical time may be influencing the relationship between tourniquet time and postoperative infections.

There is still much debate over the efficacy of tourniquet use to decrease perioperative blood loss. Ledin et al. conducted a RCT on 50 consecutive TKAs on the use of a tourniquet and found no difference in calculated perioperative blood loss [15]. The meta-analysis by Zhang et al. found that calculated blood loss was greater without the use of a tourniquet, however this did not result in a greater transfusion requirement [10]. Conversely, a meta-analysis by Jiang et al. found that tourniquet use did decrease transfusion requirement in the pooled analysis of 1,450 knees [16]. As allogeneic blood transfusion is a known risk factor for SSI and PJI, limiting blood loss is an important aspect of infection prevention [17–20].

Another concern with the use of a tourniquet during TKA is whether appropriate antibiotic prophylaxis is administered to the surgical site. Friedman et al. evaluated soft tissue and bone concentrations of antibiotics given one minute, two minutes and five minutes prior to tourniquet inflation and found the highest concentrations to be when antibiotics were administered five minutes prior to inflation [21]. Yamada et al. found that when cefazolin was administered 15 minutes prior to inflation, the concentration in bone and soft tissue at the surgical site were above the minimum inhibitory concentration (MIC90) for methicillin sensitive *Staphylococcus aureus*, but below the MIC90 for cephazolin resistant coagulase negative staphylococcal species [22]. Young et al. found that by administering antibiotic prophylaxis intraosseously, higher regional antibiotic concentrations could be achieved, however the clinical efficacy of this in reducing the rates of SSI and PJI still need to be evaluated [23].

The effect that the use of a tourniquet has on the incidence of SSIs and PJIs following TKA has not been fully evaluated. The RCTs of this subject have been of small cohorts of patients that lack the power to evaluate these complications. The meta-analyses on this topic also have not been able to definitively comment, as many studies did not report the incidence of SSI and PJI in their cohorts. Moving forward, studies evaluating the use of a tourniquet during TKA should consider SSI and PJI as a secondary endpoint so that future pooled analyses may be better able to elucidate a connection, if one exists.

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QUESTION 2: Does the surgical approach (parapatellar vs. subvastus) during primary total knee arthroplasty (TKA) affect the incidence of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: The incidence of SSIs/PJIs after primary TKA is not influenced by the surgical approach (parapatellar vs. subvastus).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 97%, Disagree: 1%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

The medial parapatellar approach and the subvastus approach are the most common approach techniques for primary TKA [1]. To date, the question of the best surgical approach for primary TKA is still a matter of debate [2]. Despite the vast body of literature investigating the clinical outcome of patients undergoing TKA with either the medial parapatellar or the subvastus approach, only a limited number of studies focus on their infection rates.

There have been four meta-analyses published to date that compare the subvastus to the medial parapatellar approach as well as one meta-analysis that compares subvastus to quadriceps-sparing approach, which are included in the following references below [1,3–6]. Regarding infection risk, none of these five meta-analyses found a difference.

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QUESTION 3: Does the surgical approach of primary total hip arthroplasty (THA) affect the incidence of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: The surgical approach in primary THA does not affect the incidence of subsequent SSIs/PJIs.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 88%, Disagree: 10%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Many approaches to expose the hip joint have been described. Surgical approaches for THA have evolved to include a minimally invasive posterior approach to minimize soft tissue damage, a resurgence of the direct lateral approach to address concerns of instability and the increased popularity of direct anterior surgery to improve postoperative recovery. Smaller skin incisions combined with less soft tissue damage and improved pain management techniques have resulted in faster recovery times, quicker rehabilitation and shorter hospital admissions. However, the impact of these approaches on the risk of infection has not been studied extensively. We report data from randomized control trials (RCT) and large registry data bases to support our conclusions.

In the English literature, 37 RCTs were found comparing functional and other postoperative results using different surgical approaches for primary THA. None of these, however, was designed to study PJI as the primary outcome. Fortunately, PJI is frequently reported as a secondary outcome. More than half of the RCTs identified (20/37) compared a conventional approach to a minimally invasive approach ("mini"), 12 studied two conventional approaches and 5 evaluated two mini-approaches. The posterolateral (PL) approach in both its standard or minimally invasive iterations were the most frequently examined (22). The primary outcome in the majority (30/36) of these RCTs was the functional assessment of the patients. The sample size of RCTs ranged from 20 to 219 THAs.

In the RCT with the greatest reported sample size, Ogonda et al. [1] followed 219 patients operated through either a standard or minimally invasive PL approach for six weeks. No infections were observed in the standard posterior approach (PA) group, while one deep and one superficial infection were found in the minimally invasive surgery (MIS) group. In another report, Xie et al. [2] studied 92 patients with unilateral primary osteoarthritis who were randomized to undergo a THA using either a supercapsular, percutaneously assisted approach or a conventional PL approach. An intention-to-treat analysis was used, but no infection was noticed in either group. Kim et al. [3] reported one infection in a study in which a mini-posterior approach was compared to a standard PL group. Goosen et al. [4], in a RCT of 120 THAs, described one infection in the "classic" group and no infections in their "MIS" group. Due to the low incidence of PJI, these trials did not have the statistical power to evaluate the relationship between surgical approach and SSI/PJI.

Eight meta-analyses [5–12] of these RCTs have been conducted to compare postoperative results of primary THA when using different surgical approaches: three compared "mini" approaches to standard ones [8,10,11], one compared mini vs. standard PL [7], one compared a direct lateral (DL) vs. the direct anterior approach (DA) [9], two compared PL vs. DA [5,6], and one compared DA, PL, lateral approaches (including the Watson Jones and modified Hardinge approaches), and two incision surgeries [12]. Two of these eight meta-analyses [6–11] were designed to specifically report significant differences in the complication rates between surgical approaches. Putananon et al. [12] performed a network meta-analysis of 14 RCTs (1,017 patients) comparing DA, PL, latera, and two incision [12] approaches and concluded that PL had the lowest risk ratio for overall complications including infection. The systematic review and meta-analysis of Miller et al. [5] was designed to compare postoperative complications of prospective and retro-

spective studies between DA and PL. A total of 7 out of the 19 studies included reported results on infection; six of them were comparative studies and one was a registry paper. PJI rate was reported as 0.2 events per 100 person-years for DA and 0.4 events for PL; this difference was statistically significant (risk ratio (RR) = 0.55, p = 0.002). However, when only the comparative studies were included in the analysis, this difference ceased to be significant (RR = 0.65, 95% confidence interval (CI) 0.16 to 2.7).

Registry data has been published that specifically looked at risk factors for revision and included surgical approach and its impact on infection risk. Due to the size of the data sets involved, registries can adjust the results to account for the impact of variables such as obesity, diabetes and hospital volume on outcomes. Recently, Smith et al. [13] retrospectively evaluated 91,585 THAs from the New Zealand Registry to identify factors that affected the infection rate following THA. Multivariate analysis revealed that the anterolateral (AL) approach significantly increased the PJI revision rate at twelve months when compared to the PL approach (odds ratio (OR) = 1.61, p = 0.005). In another study, Mjaaland et al. [14], analyzing 21,860 THAs from the Norwegian Registry, showed a significant increase in the risk of revision due to PJI when the DL approach was used, compared to DA and AL approaches (RR = 0.53), and the PL approach (RR = 0.57). However, a study [15] from the Swedish Registry showed no difference on infection rate of 90,662 THAs using either PL or AL approach, but it should be noted that no adjustment was made for obesity, Diabetes Mellitis (DM) or American Society of Anesthesiology (ASA) score. In agreement with the Swedish data is a study by Namba et al. [16] which looked at 30,491 THAs in the Kaiser Permanente Registry and did not find an association between SSI and surgical approach when adjusting for a large number of covariates such as the use of antibiotic cement, surgeon volume, age, diabetes, Body Mass Index (BMI), ASA score, and a number of other factors. However, the Kaiser Registry was composed predominantly of patients undergoing PL THA and may not have the data to comment the other approaches. Christensen et al. [17] compared 1,288 PL THAs to 505 DA patients recorded in a private registry and found a much higher incidence of wound complications that required reoperation in the DA group (1.4% vs. 0.2%, p = 0.007), but the incidence of SSI (2 in DA and 1 in PA) and PJI (1 in each group) were comparable.

Lastly, we note that obesity (a risk factor for both SSI and PJI after THA [13,16] may impact the relative risk of any specific surgical approach on infection. Watts et al. [18] stated that obesity is a stronger risk factor when the DA is used. Dowsey et al. [19], reviewed over 1,000 patients undergoing PL or DL THA. The infection rate was higher in obese than in non-obese patients when PA was used (2.5% obese and 18% morbidly obese patients), but they found no significant correlation between the DL approach and obesity. Christensen et al. [17] compared 1,288 PA THAs to 505 DA patients and found a much higher incidence of wound complications that required reoperation in the DA group (1.4% vs. 0.2%, p = 0.007), but the incidence of SSI (2 in DA and 1 in PA) and PJI (1 in each group) were comparable.

In conclusion, surgical approach does not affect the risk of SSI/PJI following primary THA. While some data exists indicating the DL and AL approaches may be at an increased risk of SSI/PJI, the data is by no means definitive. Furthermore, much of the existing data is derived from registries, which have been shown to under-report the incidence of infection [20–22]. More granular data is required in order to make a more informed conclusion on this topic.

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QUESTION 4: Does the use of periarticular injections (PAIs) affect the rate of surgical site infections/periprosthetic joint infections (SSIs/PJIs) recurrence in reimplantation?

RECOMMENDATION: Unknown. PAIs are an effective adjunct treatment for pain control following primary total joint arthroplasty (TJA), but their effectiveness and impact on the rates of SSIs/PJIs in the revision setting has not been investigated. The use of PAIs at the time of reimplantation can be performed at the surgeon's discretion.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 91%, Disagree: 5%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Pain management following primary and revision TJA is crucial to facilitate early mobilization, decrease length of stay, decrease opioid consumption and to improve patient satisfaction [1]. It is known that revision TJA cases such as prosthesis reimplantation are more complex and typically require greater dissection than primary TJA, thus postoperative pain control may be more difficult.

PAIs of anesthetic medications are a proven, effective adjunct to multi-modal pain management protocols in the primary TJA setting [1–3]. While the combination of medications injected varies widely amongst randomized controlled trials (RCTs), PAIs have been shown to provide superior pain control versus the use of patient-controlled anesthesia [4] and femoral nerve blocks [5–7], and PAIs are equivalent to the use of a femoral-sciatic nerve block following primary total knee arthroplasty (TKA) [8]. In a systematic review of 13 RCTs of patients undergoing primary total hip arthroplasty (THA), Marques et al. found patients receiving local anesthetic infiltration to have a greater reduction in pain at 24 and 48 hours postoperatively [1]. However, the impact of PAIs on pain management in the revision TJA setting, along with their impact on the rate of SSI/PJI, has not been investigated.

One consideration is whether corticosteroid should be included in the use of a PAI. There is conflicting evidence as to whether inclusion of corticosteroid in a PAI improves pain control [9–12]. Furthermore, there is the theoretical concern of a potentially increased risk of infection with the inclusion of corticosteroid given its immune-modulating properties [13,14]. No studies in the setting of primary arthroplasty have found a significant difference in SSI rates in PAI containing corticosteroid, and it is worth noting that all these studies were powered using pain as a primary outcome [9, 13,15,16]. Thus, these studies were not designed to determine the influence of corticosteroid on an outcome of low incidence such as SSI/PJI, and the risk posed by intraoperative corticosteroid PAI remains theoretical.

Unfortunately, there are no studies that assess the impact of PAIs on the rates of SSIs/PJIs recurrence during TJA reimplantation. As PAIs assist with pain control in the primary setting, it could be presumed that they are effective during TJA reimplantation, yet this has not been proven. The use of PAIs at the time of reimplantation can be performed at the surgeon's discretion, but the addition of corticosteroid should be cautioned as its immuno-modulating risk may outweigh its questionable benefit. Studies investigating the influence of PAI on the incidence of SSI/PJI following primary and revision arthroplasty are needed.

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QUESTION 5: Does simultaneous bilateral hip or knee arthroplasty (SBTHA or SBTKA) increase the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) compared to unilateral or staged bilateral arthroplasty?

RECOMMENDATION: SBTHA or SBTKA does not increase the risks of SSIs/PJIs compared to unilateral or staged bilateral arthroplasty.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 79%, Disagree: 15%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Since Jaffe and Charnley reported the first SBTHA in 1971 [1], and Ritter and Randolph performed the first detailed study of the functional outcome in 1976 [2], there has been ongoing discussion regarding the advantages and disadvantages of simultaneous bilateral procedures in the patients with bilateral arthritis.

In the absence of a randomized and prospective trial with an adequately powered sample to compare the infection rates in simultaneous bilateral joint arthroplasty with staged bilateral total arthroplasty, knowledge regarding infection rates mostly comes from retrospective studies. Many of these studies are biased, by selection bias, misclassification bias and/or follow-up time bias. Studies analyzing large numbers of patients allow for comparisons to be made regarding complications that occur infrequently, such as infection, but the validity of these comparisons is not known [3].

The reviews of the studies that analyze the probabilities of developing periprosthetic joint infection after simultaneous bilateral total arthroplasty have reported contradictory results. There have been three meta-analyses in recent years, in which the outcomes of SBTKA have been compared with staged bilateral total knee arthroplasty (BTKA). Hu et al. [4] and Hussain et al. [5] concluded that the infection rates were similar between the two groups. Other studies did not observe differences in the infection rate between simultaneous and unilateral or staged BTKA [6–15]. On the other hand, Fu et al. [16] in another meta-analysis concluded that SBTKA was associated with a lower infection rate. Similarly, Poultsides et al. [17] published the only study focused on comparing the rate of infection in a long retrospective series of patients undergoing SBTKA, staged BTKA, or unilateral total knee arthroplasty (TKA). They observed that the overall infection rate after SBTKA (0.57%) was lower compared to the staged (1.39%) or unilateral (1,1%) cohorts. The rate of superficial infection was significantly lower in the simultaneous cohort (Simultaneous: 0.28% vs. Staged: 1.04% vs. Unilateral: 0.87%; P = 0.003), but the rate of deep infection was similar among the groups (Simultaneous: 0.32% vs. Staged: 0.35% vs. Unilateral: 0.24%; P = 0.65).

Meehan et al. [18] used a more sophisticated epidemiologic methodology in an attempt to minimize the selection bias inherent in most published studies. They analyzed the California Patient Discharge database to create an intention-to-treat cohort of patients who originally were scheduled to undergo separate-admission staged BKTA. Important findings included that the SBTKA cohort had significantly lower risks of periprosthetic joint infection (odds ratio (OR) = 0.6, 95% confidence interval (CI), 0.5 to 0.7]; unadjusted rate, 8.7 per 1,000 for the SBTKA cohort compared with 16.5 per 1,000 for the separate admission staged BTKA cohort).

In a retrospective study [19], SBTKA, compared to the unilateral, was associated with increased superficial wound infection (6.0 vs. 0.7%; p = 0.003) and deep prosthetic infection (3.5% vs. 0.7 %; p = 0.02). The rationale behind these studies is that the prolonged operative time, an increased blood loss, an increased number of assistants in the operating room, changing instruments during BTKA and bilateral total hip arthroplasty (BTHA) and no redraping or rescrubbing may predispose these patients to a higher rate of infection [20,19]. Della Valle AG et al. [21] did not demonstrate a statistically significant difference in the rate of deep or superficial infections among patients undergoing simultaneous hip arthroplasty using different or the same set of surgical instruments, arguing that the use of the same set of instruments for the second side arthroplasty appeared to be safe.

Shao et al. [22] found in their meta-analysis, four studies that provided data on infectious complications (including deep and superficial infection) and the pooled data showed a statistically higher infection rate in simultaneous versus staged BTHA (OR = 2.17; 95% CI = 1.27 to 3.71; P = 0.004). In the same way, Berend et al. [23] reported a SSI complication rate of 1.8% SBTHA, which was significantly higher than the rate for staged BTHA. However, Della Valle [21] observed a 0.1% infection rate for SBTHA using the same lateral decubitus position. Other studies comparing SBTHA and unilateral total hip arthroplasty (THA) did not find increased rates of SSI [24–26]. There is only one [27] prospective, randomized, controlled study in literature comparing simultaneous bilateral and staged hip arthroplasties, and no significant difference was found in the incidence of infection between the two hip arthroplasty groups.

It is well known that simultaneous bilateral total joint arthroplasty (SBTJA) is associated with increased blood loss and need for allogeneic blood transfusion compared to unilateral or staged bilateral arthroplasty [8,23–25,27–36]. Pulido et al. [37] found, after multivariable logistic regression analysis in a retrospective study, that with simultaneous bilateral surgery (compared with unilateral procedures) the transfusion of allogenic blood units were independent predictors of PJI after primary joint arthroplasty. Nevertheless, there is contradictory evidence in the different studies on the relationship between allogeneic transfusions and the risk of PJI [38–41].

Having evaluated all available published reports, we believe that the incidence of infection following bilateral TJA (BTJA) performed under the same anesthesia is not significantly higher than the rate of infection following unilateral or staged BTJA.

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1.7. PREVENTION: PROSTHESIS FACTORS

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QUESTION 1: Are there implant materials that mitigate the risk for surgical site infections/ periprosthetic joint infections (SSIs/PJIs) after total joint arthroplasty (TJA)?

RECOMMENDATION: There are various implant materials that can be utilized to reduce the chance for SSIs/PJIs in patients undergoing TJA.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 49%, Disagree: 30%, Abstain: 21% (NO Consensus)

RATIONALE

The skyrocketing increase in number of joint arthroplasty surgeries and their associated failures have raised serious concerns in the field of medicine. Failures of medical devices due to infections have resulted in an increase in number of revision surgeries, and even fatality. Biomaterial-associated infections are fearsome complications of modern orthopaedic surgery, that often leads to prolonged

patient pain and functional losses. While immense efforts to minimize the risk of these infections have intensified over the last decade [1], orthopaedic SSIs continue to occur in worrisome numbers.

The concept of a "race for the surface" was previously proposed by Gristina [2] and Costerton et al. [3]. They described a situation whereby the ultimate fate of the implant is determined by the competition of host cells and bacterial cells. When bacteria won the race, an infection would result, instead of tissue integration. Gristina also realized that bacterial colonization of the tissue around implants was another possible mechanism of infection [2].

Herein we will review, among others, that bacterial adhesion and subsequent biofilm formation may be prevented by modifying the physicochemical surface properties of biomaterials. We will go beyond the mere aspect of implant surface biofilm formation, though. In fact, there are mainly three schools of thought regarding how to manage SSIs and PJIs. First, making the surface of the implant bacteria unfriendly; the concern about such approach is that it does not deal with infected surrounding tissue. Second, applying coatings on the implant surface that incorporate antibiotics, but coating adhesion and stability are concerns. Third, local biodegradable "implants" releasing antibiotics. We will review the benefits and limitations of each approach first. A general discussion will follow concluding that no method is ideal, but that a combination is probably needed. As is self-evident then, no consensus currently already exists.

1. Coating on the implant surface

In this strategic category the surface of the implant is coated with different materials that can release antimicrobials, including polymers, ceramics or metal oxide films. Some of the materials in this category are already on the market and clinical data are available. We will summarize these concepts first, followed by a description of concepts that are the subject of animal studies.

1.1 Gentamicin-poly (D, L-lactide) polymer coating for tibia nails

This is a fully resorbable poly (D, L-lactide) polymer with incorporated gentamicin sulphate. This material exhibits an initial burst release of 40% gentamicin over first hour and 80% of it released with first 48 hours [4].

Fuchs et al. [5] published a case study on 21 patients (13 men, 8 women) and 19 of them completed the 6-month follow-up. No implant-associated infections were seen and only one superficial wound healing was reported in one patient. Authors concluded that the use of the Unreamed Tibial Nail (UTN) PROtect® intramedullary nail was associated with good clinical, laboratory and radiological outcomes after six months.

Metsemakers et al. [6] reported another prospective case studies with the same gentamicin-poly (D, L-lactide) coating on the Expert Tibia Nail (ETN) PROtect™ on 16 patients. They described the outcome of patients treated between January 2012 and September 2013, using a gentamicin-coated intramedullary tibia nail. Treatment indications included acute, Gustilo grade II-III, open tibia fractures or closed tibia fractures with long-term external fixation prior to intramedullary nailing and complex tibia fracture revision cases with a mean of three prior surgical interventions. Outcome parameters in this study were deep infection and nonunion. Authors concluded that no deep infections occurred after placement of the gentamicin-coated nail in studied patient population.

1.2 Disposable Antibacterial Coating (DAC) hydrogel

DAC hydrogel is composed of hyaluronic acid and polylactic acid. It is supplied as powder and can be mixed with antibiotic solutions to form the hydrogel at the time of surgery. Literature data show that all types of antibiotics incorporated in DAC are released within 96 hours [7].

Malizos et al. [8] published a randomized controlled prospective study. A total of 256 patients in five European orthopaedic centers who were scheduled to receive osteosynthesis for a closed fracture, were randomly assigned to receive antibiotic-loaded DAC or to a control implant without coating. Overall, 253 patients were available with a mean follow-up of 18.1 ± 4.5 months (range 12–30). On average, wound healing, clinical scores, laboratory tests and radiographic findings did not show any significant difference between the two groups. Six SSIs (4.6%) were observed in the control group compared to none in the treated group ($P < 0.03$). No local or systemic side-effects related to the DAC hydrogel product were observed and no detectable interference with bone healing was noted.

In another multicenter, randomized prospective study, a total of 380 patients, scheduled to undergo primary (n = 270) or revision (n = 110) total hip (N = 298) or knee (N = 82) joint arthroplasty with a cementless or a hybrid implant, were randomly assigned in six European orthopaedic centers, to receive an implant either with the antibiotic-loaded DAC coating (treatment group) or without coating (control group) [9]. Overall, 373 patients were available at a mean follow-up of 14.5 ± 5.5 months (range 6 to 24). On average, wound healing, laboratory and radiographic findings showed no significant difference between the two groups. Eleven early SSIs were observed in the control group and only one in the treatment group (6% vs. 0.6%; p = 0.003). No local or systemic side effects related to the DAC hydrogel coating were observed, and no detectable interference with implant osseointegration was noted.

1.3 Silver-coated Modular Universal Tumar and Revision System (MUTARS®) for tumor mega-endoprostheses and knee arthrodesis nails

A silver (Ag) film with a thickness of 10-15 µm was deposited on the surface of MUTARS® mega-endoprostheses. This first layer was further coated with another layer of gold of 0.2 µm thick to ensure sustained release of Ag ions [10]. Hardes et al. [11] reported a prospective case study that consisted of 20 patients with bone tumors of the humerus, femur and tibia that were treated with this type of coating with an average Ag amount of 0.91 gm (range: 0.33–2.89 gm). They found that the Ag-levels in the blood did not exceed 56.4 parts per billion (ppb) and can be considered as non-toxic. Additionally, they were able to exclude significant changes in liver and kidney functions measured by laboratory values. Histopathologic examination of the periprosthetic environment in two patients showed no signs of foreign body granulomas or chronic inflammation, despite distant effective Ag concentrations up to 1,626 ppb directly related to the prosthetic surface. The authors concluded that the Ag-coated megaprosthesis allowed a release of Ag without showing any local or systemic side-effects.

In another study by Hardes et al. [10], 51 patients with sarcoma (proximal femur, n = 22; proximal tibia, n = 29) who underwent placement of a Ag-coated megaprosthesis were assessed prospectively over a 5-year period, along with the treatment administered for infection. The infection rate was compared with the data for 74 patients in whom an uncoated titanium (Ti) megaprosthesis (proximal femur, n = 33; proximal tibia, n = 41) was implanted. They found that the infection rate was substantially reduced from 17.6% in the Ti group to 5.9% in the Ag group. Whereas 38.5% of patients in the Ti group ultimately had to undergo amputation when periprosthetic infection developed, these mutilating surgical procedures were not necessary in the study group. The conclusion of the study is that the use of Ag-coated prostheses reduced the infection rate in the medium term. In addi-

tion, less aggressive treatment of infection was possible in the group with silver-coated prostheses.

1.4 Iodine-coated endoprostheses

This type of film was synthesized by using a povidone-iodine electrolyte that resulted in the formation of an adhesive porous anodic oxide with the antiseptic properties of iodine [12,13]. Shirai et al. [13] published on a study with 222 patients who suffered from postoperative infection or compromised status and were treated using iodine-supported Ti implants. The mean age of the patients was 49.4 years (range 5–85 years). One hundred twenty-seven patients were male and 95 were female. Iodine-supported implants were used to prevent infection in 158 patients who were deemed susceptible to infection. They were also used to treat active infection in 64 patients. The mean follow-up period was 18.4 months (range 3–44 months). Acute infection developed in three tumor cases among the 158 patients on preventive therapy. All three recovered without removal of the implants. Infection was cured in all 64 patients with infection. There were two patients with mechanical implant failure, which was treated by re-implantation. Excellent bone ingrowth and ongrowth were found around all hip and tumor prostheses. One year later, the amount of iodine on external fixation pins remained about 20–30%.

1.5 Thermal-sprayed silver oxide containing hydroxyapatite coating

This type of coating on the implant surface is generally prepared by thermal spraying of a mixture of silver oxide and hydroxyapatite (HA) powder using an acetylene torch. The release rate of silver (Ag) ions from this type of coating is usually high until 24 hours after immersion and decreases thereafter. Within the duration of the test, the amount of Ag ions reached 373 ppb at 168 hours [14]. Normal blood Ag concentrations are considered to be below 10 ppb [15]. Toxic side effects of Ag were described for blood concentration of 300 ppb in the form of argyrosis, leucopenia and liver and kidney damage [14,16–18]. Regarding cytotoxicity by Ag, Yamamoto et al. reported that the half maximal inhibitory concentration (IC_{50}) of Ag ion for murine fibroblasts L929 is ~458.6 ppb; further, using $AgNO_3$ for cytotoxicity test, the IC_{50} for murine osteoblastic cells MC3T3-E1 is ~298.9 ppb [19]. Eto et al. [20] recently published a first clinical study result with this implant coating. They prepared an implant for total hip arthroplasty (THA) that was coated with Ag-HA. In this study, the implant contained Ag at a maximum quantity of 2.9 mg/implant. In this prospective interventional study, THA was performed with this implant in 20 patients. They found that blood Ag levels peaked at two weeks after THA and gradually decreased thereafter. The highest blood Ag level recorded during the postoperative follow-up was 6.0 ng/mL, which was within the normal range. The Harris Hip Scores increased in all cases and activities of daily living improved markedly after THA with Ag-HA coated implants. Implant failure was absent on radiography. No adverse reaction to silver was noted and argyria was not observed in any case. No patients have developed infection after surgery. Authors concluded that Ag-HA coated implants markedly improved patients' activities of daily living without causing any adverse reactions attributable to silver in the human body. Ag-HA is expected to reduce postoperative infections and prevent decreased quality of life in patients undergoing prosthetic arthroplasty, thus leading to more favorable outcomes.

After analysis of all above mentioned clinical studies it can be concluded that more prospective randomized controlled trials that investigate postoperative infection rates of the reviewed coatings vs. uncoated control implants are needed.

Other promising approaches regarding the coating of implant with antimicrobials releasing materials are described next.

1.6 Experimental coatings

Most of the currently-available coated implants capable of releasing antimicrobials exhibit a very high initial burst release and release the majority of the drug during the first 48 hours, followed by a prolonged period of drug release at sub-inhibitory concentrations. There is a need for a coating strategy which can deliver antibiotics above minimum inhibitory concentration (MIC) level for longer duration. In this regard, Ducheyne and colleagues developed sol gel silica coating with incorporated antibiotics (vancomycin, triclosan) which exhibits the release of antibiotics above inhibitory concentration for more than four weeks. In vitro and in vivo studies in rat, rabbit and sheep showed excellent results. The in vitro study demonstrated that thin and resorbable controlled release antibacterial sol-gel films can be applied on Ti-alloy substrates. Using a multilayer process, long-term release can be achieved. The release concentrations are such that they exceed the MIC of vancomycin against *Staphylococcus aureus* [21,22]. The in vivo study with the same coating materials demonstrate that a vancomycin-containing sol-gel film on Ti alloy rods can successfully treat bacterial infections in an animal, osteomyelitis model. Radiologically, while the control side showed extensive bone degradation, including abscesses and an extensive periosteal reaction, rods coated with the vancomycin-containing sol-gel film resulted in minimal signs of infection. Micro-CT analysis confirmed the radiological results, while demonstrating that the vancomycin-containing sol-gel film significantly protected dense bone from resorption and minimized remodeling [23]. Another study by Qu et al. demonstrates that triclosan (2,4,4'-trichloro-2'-hydroxydiphenylether), an antimicrobial agent, can be successfully incorporated into micron-thin sol-gel films deposited on percutaneous pins. The sol-gel films continuously release triclosan in vitro for durations exceeding eight weeks (longest measured time point). When inserting percutaneous pins in distal rabbit tibiae, there were no signs of infection around implants coated with a micron-thin sol-gel/triclosan film. Healing had progressed normally; bone tissue growth was normal and there was no epithelial downgrowth. This result was in contrast with the results in rabbits that received control, uncoated percutaneous pins, in which abundant signs of infection and epithelial downgrowth were observed.

Another existing approach to increase the released amount of antibiotics is to combine different degradable polymers into a multilayer system. It also offers the opportunity to include multiple antibiotics that allow modulation of the release profile per antibiotic [24] and additionally degradable surfaces may be inherently resistant to infection [25]. An alternative method to obtain multilayer systems has been described by Shukla et al. who applied tetra-layers of poly-2-dextran sulfate/vancomycin/dextran sulfate by spray coating [26]. They were able to expand the release time to 100 hours.

A major problem with this strategy is the mechanical stability of the film and its adherence to the implant surface. In most of the cases, the films become damaged during the press fit of the implant. Another problem is to elute enough antibiotics for the long time.

2. Chemical modification of the implant surface

This strategy involves the direct immobilization of antimicrobials on the implant surface through chemical bonding. This approach, also known as "contact killing," works by inhibiting bacteria that come into contact with the surface of the implant. One of the approaches in this category is the immobilization of antibiotics to the implant surface. Current immobilization studies focus mainly on binding of vancomycin, which is considered to be a last

resort in treatment of infections caused by multi-resistant bacterial strains [27]. Since the working mechanism of vancomycin requires penetration of the cell wall, surface tethering is generally performed by including spacers that allow for a certain degree of freedom to penetrate the cell wall. Jose et al. used a double aminoethoxyethoxyacetate linker combined with a 3-aminopropyltriethoxysilane modified Ti surface, which produced a vancomycin surface distance of about 4 nm [28]. However, this Ti surface coating may be prone to colonization by gram-negative bacteria such as *Escherichia coli*. Therefore, to prevent infection with various bacteria, including gram-positive and gram-negative bacteria, vancomycin may not be effective by itself. Thus, an ideal Ti implant should be fabricated to combat multiple bacterial infections.

Recently Gerits et al. [29] covalently attached a new antibacterial compound a N-alkylated 3, 6-dihalogenocarbazol 1-(sec-butylamino)-3-(3,6-dichloro-9H-carbazol-9-yl) propan-2-ol (SPI031) to the Ti surface. This showed significant antibacterial activity both in vitro and in vivo without affecting adhesion or proliferation of cells involved in osseointegration and bone repair. He et al. [30] immobilized cefotaxime sodium onto the polydopamine-coated Ti through catechol chemistry. The in vitro results demonstrated that the antibiotic-grafted Ti substrate showed good biocompatibility and well-behaved haemocompatibility. In addition, the antibiotic-grafted Ti could effectively prevent adhesion and proliferation of *Escherichia coli* (gram-negative) and *Streptococcus mutants* (gram-positive).

Antimicrobial peptides (AMP) are the host-defense peptides and they are responsible for the innate immune response found among many organisms. They present significant antibacterial, antifungal, antiparasitic and antiviral activity [31–33]. Covalent immobilization of the hLf1-11 peptide on a Ti surface reduces bacterial adhesion and biofilm formation [34,35]. KR-12 (a small peptide derived from residues 18-29 of the human cathelicidin LL protein), which has antimicrobial properties and promotes human bone marrow mesenchymal stem cell proliferation at high concentrations, was used to covalently functionalize Ti; this system significantly inhibited bacterial colonization while promoting osteogenic differentiation of human bone marrow mesenchymal stem cells [36,37].

Chitosan (CS) is also explored for immobilization onto implant surfaces to improve the biological function of osteoblasts and its antibacterial performance. Covalently immobilized chitosan onto a Ti surface can first increase the antibiotic susceptibility of bacteria, limiting the internalization of bacteria into osteoblasts and preventing implant-related infection [38]. Ti modified with chitosan-lauric acid both enhanced the biological functions of osteoblasts and reduced bacterial adhesion [39]. However, interaction with a layer of protein on the CS film can lead to the loss of the antibacterial properties of CS [40,41].

3. Use of controlled release materials around the implant

In this approach, antimicrobial-loaded materials (biodegradable or non-biodegradable) are used in the space surrounding the bone implant to enhance the local concentration of antibiotics.

There has been increasing interest in products providing local antibiotic therapy. In principle there are advantages to local antibiotic use, both for treatment and prophylaxis. Buchholz et al. first popularized the incorporation of antibiotics into polymethyl methacrylate (PMMA) bone cement for local antibiotic prophylaxis in cemented TJA [42]. Clinical studies have shown that antibiotic-loaded bone cement can decrease deep infection rates of cemented total hip arthroplasties and revision rates due to supposed "aseptic" loosening when combined with systemic antibiotic administration [43] and this solution has been found both effective and economically sound, especially in high-risk patients [44,45]. However, the pharmacokinetic profile of antibiotic released from PMMA beads is far from ideal. In vitro pharmacokinetic and in vivo animal studies demonstrated a peak local antibiotic concentration on the first day followed by a drop-off by several orders of magnitude which is known as "initial burst" release. As such, a therapeutic concentration is not maintained for the desired two to three weeks [46,47]. A second major drawback is the need for a second surgery to remove the delivery system. When left in situ for too long, the beads are actually difficult to remove. A third drawback is that the continuous low dose delivery past the first day, typically at a concentration significantly below the MIC. The extended period of slow delivery can create conditions which exacerbate bacterial resistance development potential [48,49].

Due to the problem with non-biodegradable PMMA as an antibiotic carrier, many resorbable materials have been explored for local delivery of antibiotics around the implant surface.

Collagen has been extensively explored as a carrier system for antibiotics due to its biocompatibility, low costs and availability [50,51]. Commercially available products are mainly antibiotic-loaded collagen fleeces based on collagen from bovine or equine skin or soft tendon. The collagen itself is deemed hemostyptic [52]. Most commercially available products are loaded with gentamicin and release the antibiotic relatively quickly over the first few days. In vitro studies yielded a >95% of gentamicin release from collagen fleeces within the first 1.5 hours [53].

Calcium sulfate materials have been widely used as bone void filler for long time. Different types of antibiotics, such as vancomycin, gentamicin, tobramycin and daptomycin, are incorporated within calcium sulfate to explore the application as local antibiotic delivery [54]. Calcium sulfate exhibits a very high initial burst release of approximately 45 to 80% of antibiotic content within the first 24 hours [55].

Calcium phosphate materials are widely used as osteoconductive, bone bioactive materials and have excellent biocompatibility. These materials are generally used as injectable cements or as granules. The antibiotic loading can be performed in the operating room by mixing the cement together with the antibiotic agent or by soaking the granules with a liquid antibiotic solution. An in vitro release study of commercially available bone cements showed an initial burst release of active gentamicin with a relative of gentamicin of 36 - 85% for the cements and 30 - 62% for the granules. Duration release varied from one to two weeks [56].

Local delivery of antibiotics is very attractive strategy and the local antibiotic treatment options have the potential to become major tools in the treatment of bone-associated and implant-associated infections. One promising approach can be used of antibiotic-loaded resorbable carriers along with antibiotic-eluting implant. In this regard, more studies are needed to bring a viable product in the market.

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QUESTION 2: Does the type of fixation of an arthroplasty component influence the incidence of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: There is no difference in the rates of SSIs/PJIs after total hip arthroplasty (THA) or total knee arthroplasty (TKA) based on fixation of the prosthesis.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 5%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

The type of fixation utilized for an arthroplasty gets scrutinized for its functional performance and potential to reduce the incidence of subsequent SSIs/PJIs. Below is a summary of the currently available literature on the various fixation methods for primary hip and knee arthroplasty:

Cemented, uncemented and hybrid primary THA

Several randomized control studies have compared the surgical outcomes of cemented and uncemented THA. However, most of the studies were unable to reach a conclusion on the risk of PJI based on the type of fixation due to the infrequent occurrence of SSI/PJI and low number of subjects in the cohort. Among the randomized clinical trials (RCTs) comparing cemented and uncemented THA, no difference has been observed in the rates of PJI [1-6].

Because the incidence of PJI is low, an early meta-analysis did not demonstrate a statistically significant difference in the incidence of PJI based on fixation [7]. However, a more recent meta-analysis including eight clinical studies (two RCTs and six observational studies) revealed that the incidence of PJI was 0.5% (310/67,531) in cemented group, and 0.3% (47/16,669) in uncemented group ($p = 0.008$) [8]. The use of cement in THA was associated with an increased risk of PJI (odds ratio (OR) = 1.53; 95% confidence interval (CI) 1.12 to 2.10; $p = 0.008$). The possible reasons for the higher rate of PJI in cemented THA were longer operative time and the difference in patient demographics between the two groups. However, the authors could not tell the influence of the type of cement used on the risk of PJI because five of the eight studies included did not specify whether they used antibiotic-laden bone cement or not.

The most recently published report of Phedy et al. is a meta-analysis of 27 studies attempting to show whether the infection risk is higher in cemented or uncemented prostheses. By the criteria they used, they found the current evidence is low in quality and it is hard to make a definitive conclusion based on the quality of the evidence presented [9].

Registry Data:

Evidence from large population-based studies appeared to show that the risk of revision due to PJI is roughly equal comparing uncemented with cemented fixation.

A review of this question is from the Nordic Arthroplasty Register Association for patients between 1995 and 2010 revealed no difference in infection rates for cemented vs. uncemented THA, provided antibiotic-laden cement was used (relative risk 1.5 for non-antibiotic cement) [10]. Another study using the Nordic Arthroplasty Register Association in four Nordic countries (Denmark, Finland, Norway and Sweden) observed the overall risk of revision due to infection was similar for cemented, reverse hybrid and uncemented THA [11]. Using multivariable Cox analysis, the use of cement without antibiotics and hybrid configurations were found to be risk factors for infection. Data from the Swedish Hip Arthroplasty Registry (SHAR) between 1992 and 2007 demonstrated that uncemented THA did not present a higher risk of revision due to infection compared to antibiotic-laden cemented THA [12]. Another registry study in the Finnish Arthroplasty Register observed no significant differences in the risk of early revision for infection between cemented, uncemented and hybrid THA [13]. Similar results were observed in the Danish Hip Arthroplasty Register when evaluating the rate of second revision after first-time revision of primary THA with cemented and uncemented femoral components, but did note a higher percentage of the primary THA infections were from uncemented fixation [14].

In contrast to other registry studies, the New Zealand Joint Registry on primary THA done during 1999 to 2006, found a significant increase in the risk of revision for infection in the cemented (0.36%) and hybrid group (0.32%) when compared with the uncemented group (0.22%) [15]. Importantly in New Zealand, the use of antibiotic-laden cement was uncommon during this period and 64% of the revisions for infection of cemented components were in patients who did not have antibiotic-laden cement during the primary operation. Another study of primary THA from 1987 to 2007 showed a pronounced increase in the risk of being revised due to deep infection in the subgroup of uncemented THA performed between 2003 and 2007, which had an increase of 5 times (95% CI: 2.6 – 11) compared to uncemented THA from 1987 to 1992 [16]. The authors suggested that there was a trend towards higher susceptibility to deep infection for uncemented THAs than for THAs implanted with cement-containing antibiotics.

Another study from three Norwegian health registries investigated the rate of SSI and the risk of revisions due to PJI in THA [17]. During the study period from 2005 to 2009, the rate of SSI was about 3% (167/5,540), which was not influenced by cemented or uncemented fixation. Uncemented THAs had a higher adjusted risk of revision due to PJI when compared with cemented THA (risk ratio (RR) = 1.5, 95% CI 1.0 to 2.2, $p = 0.03$). The rate of revision due to PJI for hybrid fixation was not different when compared to cemented fixation (RR = 1.1, 95% CI 1.6 to 0.7, $p = 0.7$).

A Danish Hip Arthroplasty Register found patients who had received cemented THA without antibiotics (risk ratio 1.41, 95% CI: 1.01 to 1.96) and hybrid THA (risk ratio 1.53, 95% CI: 1.19 to 1.96) had a higher risk for infection relative to uncemented implants [18]. However, the same group of researchers published contradictory results of primary THA in patients younger than 55 years of age, which found uncemented and hybrid rather than cemented implants in patients younger than 55 years had more short-term revisions associated with dislocation, periprosthetic fracture and infection [19].

The higher risk of PJI in THA using plain bone cement without antibiotics was also reported by another study from the Norwegian Arthroplasty Register Association [20]. The study directly compared

the revision rates due to infection in primary uncemented THA with those of cemented THA with antibiotic-loaded cement and to those of cemented THA without antibiotic-loaded cement. The results showed that the risk of revision due to infection was the same for uncemented and cemented arthroplasties with antibiotic-loaded cement, but higher for cemented arthroplasties without antibiotic-loaded. The authors proposed that cementation might cause bone necrosis, either by direct toxicity or by the generation of heat during the polymerization process. The necrotic bone was susceptible to the growth of bacteria, which appeared to be neutralized by adding antibiotic to the cement.

Cemented vs. Uncemented TKA

Although there are several published RCTs and systematic reviews comparing the survival of cemented versus uncemented TKA, few present PJI as the primary endpoint. A Cochrane review from 2012 comparing fixation methods in TKA was unable to report on superficial or deep infection rates due to inconsistent reporting of data in the included studies [21]. Similarly, the various retrospective studies and RCTs have not demonstrated a significant difference in the incidence of PJI between the fixation methods [22-26]. However, like the studies on THA fixation, they have low enrollments and are not appropriately powered to assess for a difference in PJI.

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QUESTION 3: Does the surface (grit-blasted, plasma-sprayed, porous metal, porous beaded and hydroxyapatite (HA) coated) of uncemented total hip arthroplasty (THA) components influence the rate of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: The surface roughness, including porosity size, geometry and symmetry determines biocompatibility. Several studies have shown that the surface material influences bacterial adherence, with an ideal pore size dependent on bacterial size. Too small a pore size does not allow bacterial lodging. In recent studies, nanotexture of material has been found to be important with some surfaces with nanotubules showing anti-infective properties.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 61%, Disagree: 20%, Abstain: 19% (Super Majority, Weak Consensus)

RATIONALE

Multiple antimicrobial coatings have been proposed in total joint arthroplasty, including silver nanoparticles, sol-gel, and hydrogel synthetics, as well as direct covalent modifications of metallic and polyethylene materials. In fact, the European Commission has recently funded a four-year initiative to establish a network of institutions involved in the development of new antimicrobial coatings to prevent healthcare-associated infections [1]. Most of those efforts so far have been limited with few implants involving antibiotic doping of hydroxyapatite (HA) layers of polyethylene with long term concerns for implant survival and antibiotic resistance development.

Nevertheless, titanium (Ti) itself comes in different forms, alloys and surfaces that may present different propensities for bacterial colonization in the face of osteointegration. Most Ti implants undergo passivation before surface modification. Passivation involves the treatment of Ti by acid, electropolishing, anodizing and oxidation. The process results in surface cleaning and removal of iron and other exogenous materials, as well as a production of a surface Ti oxide layer. The side effect of passivation is often a change in surface topography and charge. Piranha etch (H_2SO_4/H_2O_2) has been previously described for passivation but significantly changes the surface topography. Prior studies have shown that hydrothermal aging was a better way of passivating orthopaedic Ti alloys as it preserved the desired surface topography [2]. The resultant Ti oxide layer is highly biocompatible and can enhance cell adhesion and proliferation [3,4]. Increased host cell biocompatibility may result in decreased infection. Gristina et al. [5] has postulated the race for the surface describing periprosthetic infection and host cell integration/biocompatibility as competing processes and suggesting as far back as 1987 that "modifications to biomaterial surfaces at an atomic level will allow the programming of cell-to-substratum events, thereby diminishing infection."

No clear quantitative research has delineated the role of nanoscale morphology on infection [6]. Several studies have examined the interaction between the surface and various proteins. This adherent extracellular matrix directly drives and signals cell interactions at the biomaterial surface. The outer membrane of a typical cell contains many receptors that look and interact with its environment at the macro- and micromolecular levels. More than 20 members of the integrin receptor family have been identified and their interaction with motifs such as Arg-Gly-Asp (RGD) within fibronectin and vitronectin have been described [7]. These receptors interact with the surface topography including grooves and ridges [8]. Nanoscale modulation of implant surface topography can drive cell adhesion, motility, activation of tyrosine kinases and gene expression. Even though it was originally thought to be the dimensions of the topographical features that determine cell interactions, the shape and symmetry of surface features are just as crucial [4]. Zinger et al. [9] has shown an impressive variety of responses dependent on the microarchitecture of the Ti surface. Osteoblasts favored larger cavities for attachment and growth, with sub-micron-scale etching enhancing differentiation. In contrast, prostaglandin synthesis was dependent on the cavity dimensions but not the sub-micron scale. Prostaglandins are important in cellular response to infection, and thus surface topography may modulate periprosthetic infection.

Interestingly, bacteria have also been shown to interact with the surface, frequently exhibiting similar propensities for biomaterials as osteoblasts. Truong et al. [10] have shown that *S. aureus* had a preference for granular Ti surfaces while *Pseudomonas* preferred polished surfaces. Singh et al. [6] show that the increase in surface pore aspect ratio and volume, related to the increase of surface roughness, improves protein adsorption, which in turn downplays bacterial adhesion and biofilm formation. As roughness increases up to about 20 nm, bacterial adhesion and biofilm formation are enhanced; further increase of roughness causes a significant decrease of bacterial adhesion and inhibits biofilm formation. Lorenzetti et al. [11] suggest that the pore size correlates to the size of the bacteria, where in, too small a size does not allow bacterial lodging into the space while too large a size does not allow the bacteria to hide from the surrounding environment and the host. Studies have shown that over 90% of *S. aureus* express either fibronectin binding proteins, fibrinogen binding proteins or collagen binding proteins, with almost 60% of bacteria expressing all of these proteins [12]. More worrisome, these genes were significantly more common in methicillin-resistant *S. aureus* (MRSA) than in susceptible strains. These cell surface receptors give bacteria an advantage for surface and extracellular matrix interactions that ultimately may allow them to outcompete osteoblasts for surface propagation.

The differential response of osteoblasts and bacteria to titanium topography raises the question regarding the specific interactions on commercially available titanium surfaces. Modern implants have gone through several iterations of surface topography changes, most recently with three-dimensional printing. Surface roughening of titanium produces topography that is biocompatible and improves osteoblast adhesion, proliferation and differentiation [13]. Much less is known about the bacterial response to these surfaces.

Grit blasting involves pressurized particle projection using ceramic or silica materials onto the implant surface. The process always involves a subsequent acid etching to remove any contaminants that could have been deposited on the surface. Al-Radha et al. [14] have examined the effect of zirconia, Ti blasted with zirconia, Ti blasted with zirconia followed by acid-etching, as well as polished Ti surfaces on bacterial colonization. The Ti blasted with zirconia reportedly showed lower bacterial adhesion, but that was in the presence of saliva. The base surfaces showed no difference in terms of bacterial colonization, even between polished and blasted surfaces. The average surface roughness in this study was about 0.16 um for the zirconia blasted surfaces.

Plasma spray coating involves thick layer deposition of materials such as Ti or HA, usually by spraying the melted material onto the substrate. Plasma spray is theoretically better controlled than grit blasting and exhibits the highest surface roughness compared to acid etching or grit blasting. Knabe et al. [15] report an average roughness of 3.43 um for plasma sprayed Ti and 2.07 for HA coated Ti. Interestingly, they also show that HA sprayed surfaces had significantly less bone contact.

HA coating is used for total hip coatings due to its presence in normal bone and the potential biocompatibility and osteoconductivity. Synthetic calcium phosphate ceramics have similar chemical and crystalline properties to biological apatite crystals. HA is the most similar to biological crystals while being the least soluble of all calcium phosphate ceramics [16]. Interestingly, in an analysis of 116,069 THAs using the Nordic Arthroplasty Register Association database, Hailer et al, [17] found no difference in revision rate between HA coated and uncemented porous or rough sand-blasted stems. Despite extensive mentioning of anti-infective properties of HA coating in the literature, the potential benefit would only be secondary to possible earlier osteoblast deposition on the surface, with no clear antibacterial effects studied or reported.

Ultimately, most studies of surface topography, surface roughening and implant surface design focus primarily on osteocompatibility. Even though surface roughness influences bacterial adhesion and survival, we were not able to identify any well controlled studies on bacterial growth on different orthopaedic implant topographies. Large registry studies show largely no difference of survival between various implants. Perhaps the material itself, such as tantalum [18], may provide an advantage in the face of periprosthetic infection. Nevertheless, roughened Ti surfaces definitely provide an osteoconductive advantage. Considering the "race for the surface" theory, such materials should then provide a certain competitive advantage against infection, even though we have a hard time recommending a specific surface topography at this time. Further research, new techniques in surface preparation, and the advantage of designer surfaces will likely allow for further delineation of this question in the near future.

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QUESTION 4: Does the type of bearing surface influence the incidence of surgical site infections/periprosthetic joint infections (SSIs/PJIs) after total hip arthroplasty (THA)?

RECOMMENDATION: There is a higher incidence of PJIs with metal-on-metal (MoM) THA; however, there is no difference in risk of PJIs among other bearing surfaces.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 84%, Disagree: 10%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

THA bearing surfaces have been developed primarily to optimize wear properties. However, there has been recent interest in differing propensities for infections among bearing types. It has been hypothesized that some bearing couples may have a disproportionately negative influence on local tissue immunocompetence, resulting in development of clinically manifested PJI that would otherwise remain silent [1].

In a study of 276,878 patients from the Australian Orthopaedic Association National Joint Replacement Registry, a higher rate of revision for PJI was observed with large-head MoM THA as compared to other bearing surfaces [2]. In a smaller retrospective case series of 124 patients, MoM THA had a 4-fold higher infection rate than historical cohorts of other bearing surfaces from the same institution [3]. Furthermore, Lee et al. performed a meta-analysis comparing MoM to ceramic-on-ceramic bearings, finding MoM bearings were associated with a higher risk of revision for PJI (odds ratio (OR) = 6.21, p = 0.015) [4].

Multiple prospective randomized trials, as well as a systematic review/meta-analysis, have demonstrated no difference in infection rate between metal-on-polyethylene, ceramic-on-ceramic, and ceramic-on-polyethylene bearings [5–8]. Hu et al. performed a meta-analysis of five randomized controlled trials comparing ceramic-on-ceramic and metal-on-polyethylene bearings and found no difference in deep infection rate [9]. A registry study by Pitto et al. found ceramic-on-ceramic bearings to have a lower risk of revision for PJI compared to other bearings [10]. However, this work did not incorporate Body Mass Index or medical comorbidities into its multivariate analysis, which are known to have a significant effect on PJI risk [11].

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QUESTION 5: Does the use of a modular femoral neck implants during primary total hip arthroplasty (THA) affect the risks of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: Modular femoral neck implants are associated with increased revision rates due to hardware failure, metal corrosion and adverse local tissue reaction (ALTR). In patients with failed THA as a result of use of a modular femoral neck, a higher incidence of subsequent SSIs/PJIs is expected.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 72%, Disagree: 21%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Modular femoral neck systems were introduced as an alternative to fixed neck systems to allow surgeons better ability to restore the biomechanics of the hip including neck angle, offset, anteversion and leg length [1,2]. However, modular femoral neck THA implants are associated with high early revision rates and poor long-term survivorships [3–8]. Reported modes of failure include hardware fracture [9–12], aseptic loosening [13] and metal corrosion resulting in ALTR [14–21]. In fact, some designs have been recalled because of high revision rates as a result of metal debris from the modular junction [3,6,22]. The additional metal junction is vulnerable to mechanical failure, component disassociation, mechanically assisted crevice corrosion (MACC) as well as metal ion release [4,5,14,17,19,20]. All modular junctions have the potential to release metal ions as a result of corrosion, wear and micromovement [2,15,18,21,23,24].

Previous literature has suggested that metal-on-metal (MoM) bearing surfaces in THA predisposed patients to higher infection rates when compared with other bearing surfaces [25–31]. It has been posited that MoM wear and corrosion particles could change the periprosthetic environment and increase the risk of infection [29]. Potential reasons for this increased risk include changes in the immune system by wear particles such as reduced cell proliferation [29,30,32]. Since modular femoral neck systems release metal wear particles and produce ALTR similar to MoM implants, are they also at risk of increased rate of PJI?

A comprehensive analysis of the incidence of SSI or PJI after the use of modular femoral necks in primary THA has not been published. Thus, the available evidence on this topic is low-level.

Duwelius et al. compared 284 patients with non-modular stems to 594 patients with modular neck stems performed by one surgeon and with similar demographics [1]. There were no statistically significant differences in either deep or superficial infection at a mean follow-up of 2.4 years (0.7% PJI in modular group vs. 1.4% in non-modular group). Furthermore, in a review of the Australian Orthopaedic Association National Joint Replacement Registry data, there was no difference in the rate of revision for infection for modular neck prostheses (0.7% of 9,289 modular neck primary THAs) compared with non-modular prostheses (0.6% of 253,165 non modular primary THAs) [8].

With the limited literature available, the presence of a modular femoral neck does not appear to increase the risk of SSI/PJI in primary THA. However, it is important to note that the clinical presentation of ALTR caused by a modular neck prostheses, head-neck junction, or MoM articulation, may mimic that of infection, and is in fact associated with a higher incidence of PJI [27,33,34] and can cause a false positive alpha-defensin test [35,36]. For this reason, gross purulence was removed from the PJI diagnostic criteria given its low specificity for PJI [37]. Thus, the reason for revision may have been misdiagnosed in some cases. In addition, many of the articles reporting higher incidence of PJI in the MoM population were before the wide acceptance of the MusculoSkeletal Infection Society/International Consensus Meeting (MSIS/ICM) definition of PJI or are Medicare database studies. PJI must be included in the differential diagnosis of all symptomatic modular femoral neck THA using recently established criteria [38].

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QUESTION 6: Can implant factors (i.e., type of bearing) influence the thresholds for serum and synovial markers in acute and chronic periprosthetic joint infections (PJIs)?

RECOMMENDATION: Yes. Different bearing surfaces such as metal-on-metal (MoM), metal-on-polyethylene and dual taper modular stems in the setting of taper corrosion can influence the serum and synovial markers. Metal debris may interfere with automated cell counts. Manual cell counts are preferred when evaluating patients for PJIs who have elevated synovial fluid metal levels. Optimal thresholds for serum and synovial markers for diagnosing PJIs in these settings still need to be established.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 97%, Disagree: 1%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

Implant factors such as bearing surfaces can influence serum and synovial markers when evaluating for PJIs. This has been mostly studied in MoM bearings and dual taper modular stems [1–3]. It can be difficult to discern adverse local tissue reactions (ALTRs) with associated metal ion release from inflammatory response to infection [4,5]. However, it is important to determine the presence of infection as it will alter treatment [6,7]. Serum erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and white blood cell (WBC) count with differential are important tests in helping determine presence of PJI [8].

There have been various recommendations regarding the parameters for serum and synovial markers for diagnosing PJI in the presence of MoM corrosion, but most studies have demonstrated that the type of bearing surface and other implant factors can affect the thresholds for serum and synovial markers in PJI. Still, no literature has clearly delineated the specific parameters that should be utilized for differing bearing surfaces to diagnose PJI [9,10].

Automated synovial cell counts and differentials in the setting of a failed MoM THA have been reported to be inaccurate [2,3,11]. It has been theorized that the automated cell counting machine may be incorrectly identifying particulate debris and counting it as cellular [2]. As such, many surgeons propose utilizing a manual cell count and differential when analyzing the synovial WBC and differential [1].

Wyles et al. [2] found that the sensitivity of the synovial WBC count could be maintained at 100% while improving specificity to 71% if the cutoff to diagnose infection was moved from >3,000 to >15,000 cells/microliter. Additionally, the authors found the sensitivity of neutrophil percentage could be maintained at 100% and improved specificity to 100% by elevating the cutoff percentage from 82 to 92% neutrophils. Regarding CRP, the authors found that the sensitivity of CRP could be maintained at 75% while improving the specificity of CRP to 97% if the cutoff value of CRP was raised from >8 to >54 mg/L. The authors demonstrated that changing the cutoff value for the ESR did not change specificity as significantly.

In contrast, Yi et al. [3] studied PJI in patients with failed MoM bearing surfaces and after excluding what they deemed to be inaccuracies, recommended a synovial WBC cutoff of 4,350 WBC/microliter with 100% sensitivity and 95% specificity. The authors, however, reported low positive predictive values of 43% and 39% for ESR and CRP, respectively, in the setting of MoM bearings.

Kwon et al. reported that ESR and CRP have a limited value in the diagnosis of PJI in dual taper modular implants with evidence of corrosion, but acknowledged the utility of ESR and CRP in excluding PJI [1]. The authors demonstrated, however, that synovial WBC and differential were useful markers for diagnosing infection. Specifically, the authors demonstrated a sensitivity and specificity of 86% and 80%, respectively, when utilizing a synovial WBC cutoff of 730 cells/microliter. A synovial polymorphonuclear (PMN) % cutoff of 65% yielded a 100% sensitivity and a 70% sensitivity.

Okroj et al. in a multicenter study evaluated the alpha-defensin test to diagnose PJI in the setting of ALTRs. Twenty-six patients were reviewed with one of 26 (3.8%) meeting the MusculoSkeletal Infection Society (MSIS) criteria for PJI. The one patient with PJI had a metal-on-polyethylene bearing surface with head-neck taper corrosion. Of note, there were 8 falsely positive alpha-defensin tests. The authors concluded that in the setting on ALTRs, alpha-defensin testing can lead to a high rate of false positives [12].

Though the exact parameters to diagnose PJI in the setting of different implant factors need further elucidation, given the existing literature, we conclude that various implant factors can influence both synovial and serum markers in the setting of PJI. We strongly urge the orthopaedic community to be cognizant of the influence of bearing surfaces, especially in the setting of MoM implants or potential metal corrosion, and to consider using a combination of diagnostic tests along with manual cell counts as part of their PJI diagnostic workup.

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QUESTION 7: What can be done with a prosthesis that has been dropped on the floor or allowed to come into contact with a non-sterile portion of the operating room?

RECOMMENDATION: Cleaning, re-sterilization and reuse of dropped prostheses or implants is not permitted in most hospitals and should not be performed. Only in extremely rare circumstances, such as the use of a custom implant, a dropped prosthesis may be decontaminated and sterilized.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 90%, Disagree: 8%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

The creation and maintenance of an aseptic environment has a direct influence on patient outcomes in general and the incidence of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) in particular. One of the measures for preventing SSIs is to provide surgical instruments and implants that are free of contamination at the time of use [1]. This is particularly important when an implant such as a joint prosthesis is being left behind in the body. Prior studies have shown that as little as 100 bacteria gaining access to a surgical field that involves the use of an implant is sufficient to lead to infection [2,3]. The number of bacteria needed to result in infection in the absence of an implant was much higher [4,5]. Thus, the presence of a foreign material, such as an implant, is a strong risk factor for subsequent SSIs/PJIs [4,5]. Due to this, extreme care should be exercised in ensuring that the prosthesis being implanted in joints are completely sterile and devoid of any bacteria [6].

There are strict regulatory requirements for implant sterilization, which is usually the last step in manufacturing of these prostheses [7]. Most manufacturers use high dose gamma irradiation to achieve the required sterility of implants manufactured for use in humans [6]. Implants being opened from their package are thus believed to be absolutely sterile. Dropping an implant on the floor results in contamination of the implant by microorganisms that can potentially lead to a subsequent infection. Sterilization of the dropped implants in the hospital using autoclave does not meet the regulatory requirements and very likely leads to presence of residual bacteria or their cell walls "exotoxins" [8]. Thus, this practice is not considered to be acceptable by hospitals and local health authorities.

Different sterilization methods, such as steam, dry-heat, ethylene oxide, formaldehyde or ionizing radiations result in a different effect on the biomaterial surface and their subsequent behavior in vivo [9]. Titanium (Ti) has been widely used as an implant material due to its biocompatibility and excellent corrosion resistance. In order to enhance osseointegration of dental and orthopaedic implants made of Ti, many surface modification strategies have been pursued, focusing on the important role of the biomaterial surface properties [6].

Annunziata et al. evaluated the effects of the argon plasma treatment on different Ti implant surfaces previously exposed in vitro to bacterial contamination. They found that the argon plasma technology could be efficiently used to decontaminate/sterilize previously contaminated Ti implant surfaces [7], however, they did not evaluate any possible adverse effect of sterilizing method on implant characteristics. Park et al. evaluated the effect of cleaning and sterilization on Ti implant surface properties and cellular response. In their study, different methods for Ti sterilization that included autoclaving, gamma irradiation, oxygen plasma, and ultraviolet were used [6]. The study indicated that recleaning and resterilized Ti implant resulted in surface alterations that could potentially affect the osseointegration of the surface and other biological behavior of the biomaterial in vivo.

Based on the latter study, we conclude that resterilization of dropped components in a hospital setting could lead to detrimental alteration of the biomaterial surface of the implant being used and adversely affect the in vivo behavior of the implant. Thus, and whenever possible, a new implant should be used to replace the dropped implant. If this is not possible, the dropped implant needs to be processed very carefully to remove all potential microorganisms on the surface [10]. This may include chemical cleansing of the implant with bactericidal agents such as chlorhexidine or povidone iodine. The purpose of cleaning is to remove or reduce visible soils, blood, proteins and debris [11]. To resterilize the implant, it should be subjected to steam-heat, as irradiation method for sterilization is not available in hospitals. Flash sterilization is not recommended [1]. The wound should also be copiously irrigated with antiseptic solution, such as aqueous povidone iodine, prior to the use of the dropped implant.

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1.8. PREVENTION: POSTOPERATIVE ISSUES

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QUESTION 1: Should patients with cellulitis following total joint arthroplasty be treated with antibiotic therapy?

RECOMMENDATION: Yes. When periprosthetic joint infection (PJI) has been ruled out, it is reasonable to treat patients presenting with cellulitis with empiric antibiotics.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Much of the literature relating to infectious postoperative complications relates to deep PJIs. Postoperative cellulitis is a rare, yet realistic complication that may occur following arthroplasty. The concern for cellulitis is that the superficial infection may spread to the deeper tissues including the prosthetic joint. Thus, the presence of cellulitis in patients with a prosthetic joint is considered to be a serious issue.

All the literature relating to the treatment of superficial infections relates to hip and knee arthroplasty. Many of the studies in this area are of non-randomized, retrospective designs. Much of the literature related to surgical site infections (SSIs) in total joint arthroplasty is epidemiological in nature, focusing on incidence and risk factors, rather than treatment and outcomes. Perhaps reflecting the diagnostic dilemma facing physicians, there appears to be much heterogeneity in the literature in defining the diagnosis of cellulitis versus inflammation versus superficial SSIs.

The largest prospectively gathered dataset regarding superficial wound infections has been described by Guirro et al. in a Spanish cohort following total knee arthroplasty (TKA) [1,2]. They highlight 45 cases of superficial wound infections in a larger series of 3,000 joints with six years follow-up, without any evidence of recurrence of infection or progression to deeper periprosthetic infections. Of note, is that six (13.3%) of these patients also required surgical treatment in the form of wound irrigation and debridement in addition to antibiotic therapy. Interestingly, three of these patients required later revision arthroplasty for non-infectious causes.

The occurrence of an erythematous, erysipelas-like manifestation after total hip arthroplasty (THA) has been described in two publications [3,4]. A total of 17 patients across both publications were described as successfully treated with antibiotics following an erythematous eruption around the incision and the gluteal area. There was no evidence of a deep infection at last follow-up.

Walls et al. described a case series of methicillin-resistant *Staphylococcus aureus* (MRSA) SSIs following primary hip arthroplasty [5]. Out of 1,790 hips performed over a five-year period, 18 (1%) were described as having MRSA SSIs. Six of these 18 were defined as superficial infections. Five were treated successfully with antibiotics, while one patient returned after seven months with a deep infection.

The other series described in relation to TKA has been published by Manian et al. [6]. Of note, this was a retrospective case series evaluating post-arthroplasty patients presenting with any form of soft tissue or skin bacterial infection in the lower limb. Interestingly, at a mean of 65 months postoperatively, patients were statistically more likely to present with cellulitis in the operated limb than their contralateral leg. They did not define their treatment outcomes.

It is clear from this discussion that there is a marked heterogeneity in the literature regarding the use of antibiotics in patients with cellulitis post-arthroplasty. Without clear consensus on defining the diagnosis, in addition to the myriad of study methodologies, the data is not amenable to meta-analysis. To determine a more robust consensus on this question, further prospective randomized trials are recommended.

In the absence of such studies and evidence, we feel that cellulitis is a serious event in patients with a prosthetic joint in place and requires treatment. However, to distinguish cellulitis or superficial infection from PJI is a difficult task in a majority of patients. As missing the diagnosis of PJI may result in suboptimal outcomes for patients because they are not usually amenable to treatment with antibiotics alone, we recommend that any patient presenting with cellulitis or presumed superficial infection undergo an evaluation for a PJI, which may include aspiration of the joint in order to rule out a PJI prior to empiric antibiotic treatment.

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QUESTION 2: Is undergoing a colonoscopy or upper gastrointestinal (GI) endoscopy after total joint arthroplasty (TJA) associated with an increased risk of surgical site infection/periprosthetic joint infection (SSI/PJI)? If yes, does antibiotic prophylaxis prior to a colonoscopy or upper GI endoscopy after TJA reduce the risk?

RECOMMENDATION: Colonoscopy and upper GI endoscopy have the potential to cause transient bacteremia, though the evidence is limited to support an associated risk of SSI/PJI. There is no evidence that administration of antibiotics prior to GI procedures decreases the risk of SSI/PJI and this practice should be avoided. Further research is needed to see if this practice may be beneficial in selected or high-risk patients.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 84%, Disagree: 13%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Transient bacteremia can occur with many procedures, including periodontal manipulation, barium enema and GI and genitourinary (GU) procedures. Endoscopic procedures, including colonoscopy and esophago-gastro-duodenoscopy (EGD), are frequently associated with transient bacteremia [1–5]. The incidence of bacteremia after standard colonoscopy has been estimated to be between 0 and 5% [6]. Rates of bacteremia increase when endoscopy is accompanied by instrumentation and tissue manipulation, such as biopsy or polypectomy and the incidence of bacteremia differs by procedure: flexible sigmoidoscopy 0.5%, colonoscopy 2.2%, EGD 4.2%, variceal ligation 8.9%, endoscopic retrograde cholangiopancreatography (ERCP) 11%, variceal sclerotherapy 15.4% and esophageal dilation 22.8% [7]. Another study showed similar results with the highest rates of bacteremia occurring with dilation of esophageal strictures and sclerotherapy of esophageal varices (approaching 45%) [2].

Although it is recognized that transient bacteremia does occur after GI endoscopic procedures, the same phenomenon occurs frequently during routine daily activity, often at rates exceeding those associated with endoscopy. EGD with dilation has been associated with transient bacteremia rates of 12 to 22% [7,8], whereas, brushing and flossing teeth has been associated with bacteremia rates between 20 to 68%. Even routine activities such as mastication have been associated with bacteremia rates of 7 to 51% [9]. These high rates compared to the relatively low frequency of bacteremia in patients undergoing GI procedures has been the rationale for the American Society for Gastrointestinal Endoscopy (ASGE) advocating that routine prophylactic antibiotics prior to endoscopic procedures in patients with orthopaedic implants is not required [10].

Evidence is lacking to support an increased risk of SSI/PJI from colonoscopy or upper GI endoscopy. There is one prospective single-center, case-control study conducted by Coelho-Prabhu et al. that found a possible increased risk of PJIs among patients undergoing EGD with biopsy (odds ratio (OR) =3, 95% confidence interval (CI): 1.1-7) [4]. Cases were defined as adult patients hospitalized for PJI of the hip or knee between 2001 and 2006. Controls were adults with hip or knee arthroplasty without a diagnosis of joint infection who were admitted during the same interval. There were 339 identified cases and 339 controls. The primary outcome measure was the odds ratio of PJI after a GI endoscopic procedure performed within the last 2 years. Procedures included flexible sigmoidoscopy, esophageal dilatation and EGD and colonoscopy both with and without biopsy. Overall, there were 21% of case patients who underwent a procedure vs. 24% among the controls. Among the procedures, only EGD with biopsy was found to have a significant association with PJI. EGD with biopsy had occurred in 19 (6%) of cases and 8 (2%) of controls (OR 2.8). After adjusting for various risk factors, the OR for PJI after EGD with biopsy was 3.8 (95% CI: 1.5-9.7). Among the PJI cases, there was no significant difference in the microbiology of PJI between the group who had undergone endoscopy and the group that did not. Both groups had coagulase-negative *Staphylococcus* species and *Staphylococcus aureus (S. aureus)* as the most common organisms, whereas, bacteria colonizing the GI tract comprised only 17% of PJIs in both.

Another study by Ainscow et al. prospectively studied 1,000 patients who underwent 1,112 hip and knee arthroplasties over six years [11]. These patients were not advised to take antibiotic prophylaxis for subsequent dental or surgical procedures. A total of 224 had undergone dental or surgical procedures. Only three cases of hematogenous infection had developed during the study period, all from a skin or soft tissue infection source [11].

In addition to the above, there have been only four case reports in the literature describing a PJI that occurred within 12 hours to 2 weeks of an endoscopic procedure [12–15]. The bacterial pathogens that were believed to have hematogenously spread to the prosthetic joint in these cases included *Streptococcus milleri*, *Group B streptococcus, Listeria monocytogenes,* and *Serratia marcescens*. Notably, these case reports were published from 1990 to 2003, when orthopaedic and gastroenterological practices differed from the current practices in 2018.

In summary, there is no clinical evidence that giving prophylactic antibiotics decreases the risk of SSI/PJI after colonoscopy or upper GI endoscopy procedures. Before deciding to give antibiotic prophylaxis, clinicians must evaluate each patient individually based on the risk factors and type of procedure and balance the benefits of antibiotic prophylaxis with the risks of increasing bacterial resistance, adverse side-effects and drug interactions.

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Diagnosis

2.1. DIAGNOSIS: DEFINITIONS

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QUESTION 1: What is the definition of a periprosthetic joint infection (PJI) of the knee and the hip? Can the same criteria be used for both joints?

RECOMMENDATION: See Figure 1, Proposed 2018 International Consensus Meeting (ICM) criteria for PJI.

Major Criteria (at least one of the following)	Decision
Two positive growths of the same organism using standard culture methods	Infected
Sinus tract with evidence of communication to the joint or visualization of the prosthesis	

Minor Criteria	Threshold		Score	Decision
	Acute€	Chronic		
Serum CRP (mg/L) *or* D-Dimer (ug/L)	100 Unknown	10 860	2	Combined preoperative and postoperative score: ≥6 Infected 3 to 5 Inconclusive* <3 Not Infected
Elevated Serum ESR (mm/hr)	No role	30	1	
Elevated Synovial WBC (cells/µL) *or* Leukocyte Esterase *or* Positive Alpha-defensin (signal/cutoff)	10,000 ++ 1.0	3,000 ++ 1.0	3	
Elevated Synovial PMN (%)	90	70	2	
Single Positive Culture			2	
Positive Histology			3	
Positive Intraoperative Purulence¥			3	

€This criteria were never validated on acute infections. ¥ No role in suspected adverse local tissue reaction.
*Consider further molecular diagnostics such as next-generation sequencing

FIGURE 1. Proposed 2018 ICM Criteria for PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 68%, Disagree: 28%, Abstain: 4% (Super Majority, Weak Consensus)

RATIONALE

The introduction of the MusculoSkeletal Infection Society (MSIS) criteria for PJIs in 2011, which was later altered by the 2013 ICM, resulted in immense improvements in diagnostic confidence and research collaboration [1]. In recent years, numerous serum and synovial markers have been evaluated and have become widely available [2–14]. Moreover, publications in recent years show different sensitivities and specificities for the various tests used [4,14] and highlight the value of a high pretest probability in the overall diagnosis [9,15,16]. These advancements in the field call for the modification of current diagnostic criteria to an evidence-based one.

In a recent multi-institutional study [17], we proposed a new definition considering the relative and quantitative weight of established, as well as newer, markers [7,9,11]. The new diagnostic criteria also consider chronicity and invasiveness of the diagnostic tests, making the preoperative diagnosis of infection easier compared to previous definitions. By using a stepwise approach in developing the current criteria which was based on the current American Academy of Orthopaedic Surgeons (AAOS) guidelines [18], we were able to provide relative weights for each diagnostic marker/finding. The threshold for infection of the combined score was determined in a way that would keep false positives to a minimum (threshold for infection), but also reduce false negatives (threshold for not infected). By performing this in a stepwise manner, we were able to maximize sensitivity in early stages of the workup (to avoid under-diagnoses), as well as to maximize specificity in later stages (to avoid over-diagnoses).

This proposed definition showed a high level of performance using an independent multi-institutional cohort for validation and a better performance compared to previous MSIS and ICM definitions. The new criteria demonstrated a sensitivity of 97.7% compared to the MSIS (79.3%) and ICM definition (86.9%), with a similar specificity of 99.5%. It also enabled one to reach an earlier diagnosis compared to previous criteria, as more than 80% of the PJI cases using the new definition were diagnosed prior to surgery. This enhanced the importance of a joint aspiration prior to surgery and supported it in becoming the cornerstone of diagnosing PJIs. Another novel finding of the present definition is the introduction of patients in which a diagnosis is inconclusive. These patients are often encountered in clinical practice and represent a real diagnostic challenge. Pointing out this unique group or "gray area" of patients promotes awareness in both clinical practice and the need for further research focused on this cohort.

ICM Discussion and Controversies

The criteria have been reviewed and altered by a group of recognized international experts who were also delegates of the ICM. This question and the proposed criteria have been discussed and debated extensively during the ICM and reached only a weak consensus, with 28% disagreeing with it. Our group wishes to point out some important clarifications and controversies that were raised during the meeting:

1. The proposed definition was developed and validated on a cohort with chronic PJIs. Patients with acute PJIs and acute hematogenous PJIs (with < 6 weeks of symptoms) were excluded from this study since we were not able to define a proper control group for them. A control group for acute infections would be patients following joint arthroplasty undergoing a serum and synovial fluid investigation, but proven to not be infected—isolating and defining the control cohort is challenging and rare. Different thresholds for acute infections have been suggested in the literature and we used the previous ICM thresholds for the parameters used. While we believe these new criteria should apply also for acute and acute hematogenous infections, both the scoring system and the proposed thresholds require further validation on this specific population.
2. The proposed criteria may under-diagnose less overt infections. Defining PJIs based on major criteria for developing the scoring system may have affected the thresholds of different markers and has the potential to under-diagnose more overt infections. That being said, 30% of the cohort used for developing the scoring system had Coagulase-negative Staphylococcus (CoNS), which is not considered to cause a major immune response. Moreover, we validated the scoring system on an external cohort of infected and non-infected patients, independent from any previous criteria. In this group of patients, there were many culture negatives as well as so called "low grade infections," and the new criteria demonstrated a high sensitivity of 97.7%. Future research should be aimed on validating the utility of the new definition in more overt infections.
3. For the current definition, a decision tree index (Gini) was used to point out the thresholds for the various markers evaluated that would provide maximal sensitivity and specificity for each marker based on chronicity and the pretest probability. When these thresholds were similar to the previous ICM definition, we used the earlier one to ease its implementation. It should be pointed out that a variety of thresholds have been proposed in the literature and may be different from the ones proposed here. These differences may be attributed to the fact that we wanted to maximize sensitivity in early stages of the workup and to maximize specificity in more advanced stages.
4. The new diagnostic criteria were originally validated on patients from three major orthopaedic institutes in the United States. Additionally, since its introduction earlier this year, the criteria have been validated in patients treated in Japan and Brazil, as well as 84 patients from around the globe using a designated chatbot. They need to be further tested and validated in large volume centers outside the USA to assess whether the preliminary findings presented above are indeed accurate.
5. Several delegates have raised the issue that alpha-defensin is an expensive test that should not be performed routinely. We would like to emphasize that the present scoring system is not designed or intended to be used as a guide for which tests should be ordered; rather, it should be used as a tool to diagnose patients when a panel of tests are already available. Not all tests are needed to use this proposed definition and a preoperative diagnosis can be made without the need for intraoperative findings. To further clarify this issue, we have combined the two tables from the original criteria (separating preoperative and intraoperative findings) into one table.
6. In the present study, we used conventional cultures to diagnose and to define positive growth. We did not use sonication or novel techniques such as Next Generation Sequencing. More sensitive microbiological investigation methods are likely to reveal a potential infection in the absence of elevated serum and/or synovial markers. As these novel methods for isolation of organisms become more widespread, the newly proposed criteria should be validated once again.

7. The proposed definition was developed and validated on both PJI cases of the knee and the hip. While several publications have noted differences in the thresholds for synovial markers in PJI cases of the hip and the knee, we believe the differences are minor. Thus, the new definition has not made a distinction between hip and knee PJI. Nevertheless, future studies should explore such potential difference between these two joints.
8. Newer markers, such as the serum D-dimer, have not been sufficiently studied and while we had sufficient data to analyze the new markers and include them in the definition – more work is needed to further validate their role in the diagnosis of PJIs. Moreover, their role and thresholds in diagnosing acute PJIs still remains unknown.
9. In patients with adverse local tissue reactions (ALTRs), crystalline deposition arthropathy, inflammatory arthropathy flares, infections with slow-growing organisms and patients under antibiotic treatment, the proposed criteria may be inaccurate.
10. There may be other situations when a patient is infected and does not meet the diagnostic criteria and vice versa. Clinical judgment should still prevail and guide physicians in the management of patients.

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QUESTION 2: What is the definition of septic arthritis in a native knee?

RECOMMENDATION: Native septic arthritis of the knee is a clinical diagnosis supplemented by relevant laboratory data. Signs of septic arthritis include painful effusion, limited range of motion and warmth. Elevated serum inflammatory markers, particularly C-reactive protein (CRP), synovial white blood cell (WBC) counts (50,000 cells/mm^3), polymorphonuclear (PMN) cell count percentages (> 90%) and purulent appearance of the synovial fluid indicate a high likelihood of septic arthritis.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 7%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Native septic arthritis of the knee classically presents with a painful effusion and limited range of motion. Diagnosis of this clinical entity cannot be made on the basis of laboratory data alone, with infections occurring in the presence of negative cultures and absent in the presence of markedly elevated intra-articular cell counts [1]. The frequency of native knee septic arthritis appears to be increasing and major concerns for serious medical complications and mortality persist [2]. The most robust information on laboratory data diagnostic for septic arthritis is available for the pediatric hip joint [3,4]. However, such high-quality, algorithmically predictive data is lacking for the adult native knee joint.

Septic arthritis in the knee remains a challenging diagnosis to make due to similarities to other entities in clinical presentation and equivocal laboratory results. Clinical impression remains the mainstay of diagnosis, but should be supplemented by relevant laboratory data. Screening inflammatory markers, particularly a

CRP, should be obtained and suspicion for infection should always be kept to avoid missing a diagnosis. Aspiration of the knee should be completed prior to administration of antibiotics when clinically feasible to increase diagnostic accuracy. Synovial cell counts greater than 50,000 cells/mm^3 and/or PMN cell count percentages greater than 90% indicate a high likelihood of septic arthritis [5].

Laboratory data obtained where clinical suspicion for septic arthritis exist includes serum erythrocyte sedimentation rate (ESR) and CRP. While lacking specificity, a CRP elevated above 10.5mg/dL has been demonstrated to show a high correlation with septic arthritis in native joints in the appropriate clinical scenario [6]. A study by Hügle et al. also indicates that procalcitonin (PCT) is useful for establishing the presence of infection and may have superior sensitivity and specificity than CRP in detecting septic arthritis [7].

Aspiration is a critical portion in evaluating the possibility of native knee septic arthritis. Numerous studies and a meta-analyses have shown higher synovial WBC counts more likely to represent infection [8] and greater percentage of PMN cells (> 90%) highly predictive of septic arthritis [5]. Traditional teaching held that cell counts could be divided into non-inflammatory, inflammatory and infectious, corresponding to 0 to 2,000 cells/mm^3, 2000 to 50,000, and >50,000, respectively. However, one investigation showed only 64% sensitivity of using this infectious cell count cutoff, with approximately one-third of patients with septic arthritis having a cell count lower than 50,000 [9]. Therefore, infection can also be present with lower cell counts and gross inspection of the fluid can be as valuable as the cell count in determining infectious pathology of an effusion [10,11]. In particular, synovial WBC count more than 50,000 and percentage of PMN more than 90% provide adequate concern to identify septic arthritis while waiting for culture test results [5].

A native knee aspiration resulting in a false positive culture is rare if done under proper technique. Jennings et al. demonstrated a false positive rate of 0% of 166 knees in their series using appropriate sterile technique [12]. Therefore, positive cultures obtained using such technique should raise the alarm for the high likelihood of a real infection. Administration of antibiotics prior to obtaining an aspiration has been shown by Hindle et al. to decrease the yield for culture and to reduce its accuracy from 79 to 28%, and should be avoided when feasible [13]. The available literature suggests that Staphylococcal species are the most common causative organisms for septic arthritis of the knee in an adult, followed by other gram-positive cocci and gram-negative bacilli [2,14]. However, septic arthritis by other atypical organisms can occur and this needs to be kept in mind when investigating patients with suspected septic arthritis.

The leukocyte esterase (LE) test is used commonly for diagnosis of infections in different organs [15]. In a recent prospective study of 27 cases of acute monoarticular arthritis in major joints, Gautam et al. reported a 100% sensitivity of the LE test in the diagnosis of septic arthritis when +2 was considered indicative of a positive result. The positive predictive value in their series was 94% and only one synovial sample was LE positive despite negative culture results. They concluded that this test could efficiently differentiate other etiologies of inflammatory acute arthritis from septic arthritis [6]. Another study by Ceja-Picazo et al. had almost identical findings and supported the use of LE dip stick in investigation of patients with painful knee and suspected of septic arthritis, as it was able to differentiate osteoarthritic from infected knees [16].

The role of molecular techniques such as polymerase chain reaction (PCR) has been previously investigated in the diagnosis of septic arthritis. The studies have found that PCR may not provide additional data to culture in investigation of these patients [17]. However, as time has progressed and technology has improved, molecular techniques are likely to play a critical role in the diagnosis of orthopaedic infections in general and septic arthritis in particular [18,19]. The newer molecular techniques such as next generation sequencing, because of the rapid decline in DNA sequencing costs, are likely to be even more beneficial in the investigation of patients with orthopaedic infections. These tests will result in a notable decrease in time to diagnose the condition and to isolate the causative organism.

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QUESTION 3: How can superficial surgical site infections (SSIs) be differentiated from deep SSIs (i.e., periprosthetic joint infections (PJIs))?

RECOMMENDATION: There is no single objective clinical test or imaging approach established for the differentiation between a superficial SSI, a deep SSI and a PJI. We recommend that clinical evaluation, workup for infection and early joint aspiration should guide the decision.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 3%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

SSIs are infections at the incision site occurring within 30 days after surgery or within one year if implants are left in place [1,2]. The definition commonly used for SSI was specified by the Centers for Disease Control and Prevention (CDC) criteria in 1999 [1]. They are generally categorized into superficial incisional, deep incisional and organ/space SSIs [2,3]. Parvizi et al. proposed a new (2018) definition for PJI (see Question 1, Fig.1) [4]. The new scoring-based definition updated the previous one [5] and is evidence-based with externally validated criteria.

Comparing the aforementioned definitions, CDC criteria for diagnosing SSIs are mainly based on clinical evaluations and histopathology findings, while criteria for diagnosing PJIs also include laboratory results. There is no clinical, laboratory or imaging procedure to reliably allow differentiation between SSIs and PJIs or even between the three different subtypes of SSIs. Furthermore, diagnostic criteria for superficial SSIs, such as tenderness, redness, localized swelling and local heat, have low inter-observer reliability [6]. In the CDC definition, fever above 38° Celsius is considered a clinical sign of a deep incisional SSI [2]. Other wound scoring systems also exist, such as ASEPSIS (Additional treatment, Serous discharge, Erythema, Purulent exudate, Separation of the deep tissues, Isolation of bacteria, and Stay as inpatient prolonged over 14 days). However, neither the CDC definition, nor ASEPSIS differentiate superficial from deep incisional and organ/space SSIs [7]. Additionally, a low-volume knee study demonstrated clinical wound scores (Surgical Wound Aspect Score) with superficial infections having lower scores than deep infection [8]. Despite this finding, the observed difference was not statistically significant [8].

We can assume that PJIs correspond to organ/space SSIs and subsequently, we can attempt to differentiate between superficial SSIs and the organ/space SSIs in a total joint arthroplasty (TJA). A working group of the federal Healthcare Infection Control Practices Advisory Committee completed a comprehensive review of National Healthcare Safety Network (NHSN) SSI definitions in 2011 and 2012. They supported the NHSN adoption of the ICM on PJI's definition of a PJI as the hip and knee arthroplasty "organ/space" SSI [9].

A leaking wound following an arthroplasty can be either the result of a hematoma, seroma, fat necrosis or a sign of deep infection and could also be a risk factor for PJIs (odds ratio (OR) 35.9; 95% confidence interval (CI), 8.3–154.6) [10,11]. Persistent wound drainage may be contaminated and result in a deep infection [12–14]. This knowledge led the 2013 ICM to propose surgical treatment of wound drainage within five days after the index procedure [15]. In a review by Zimmerli, it was proposed that classification of the SSI should guide the selection of the optimal surgical management [16]. An infection occurring within one month of an invasive procedure, such as TJA or arthrocentesis, was classified as an early post-interventional PJI [16]. An acute hematogenous PJI occurs after an uneventful postoperative period with symptoms lasting three weeks or less [16]. Chronic PJI is defined as an infection with symptoms persisting for more than three weeks, or a SSI diagnosed later than one month after implantation [16]. Early post-interventional and acute hematogenous PJIs generally are able to be treated with implant-retaining measures, while chronic PJIs require prosthesis removal due to biofilm formation [16].

A literature review was conducted that revealed no single objective, non-invasive clinical test or imaging approach which can differentiate between a superficial SSI and an early deep PJI. Although several studies address the risk factors for SSI or PJI, none of them differentiated these two conditions [9,17]. We recommend that clinical judgment and early joint aspiration should guide the decision to perform a debridement, antibiotics and implant retention (DAIR) procedure or a superficial debridement. Due to the devastating consequences following PJIs, we recommend that surgeons should have a low threshold for performing a DAIR procedure. Surgeons should also differentiate between stitch abscess, which has only minimal inflammation or discharge from suture points, and superficial and deep surgical site infections. This differentiation can guide the surgeon to perform the needed intervention. Patients in whom the deep space is not involved can be subjected to superficial irrigation and debridement only. In contrast, a DAIR procedure is preferable in patients with deep infections.

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QUESTION 4: How can hip septic arthritis be differentiated from toxic synovitis?

RECOMMENDATION: Currently, there is no single diagnostic test or step that can be performed in order to distinguish a patient with a septic hip from one with toxic synovitis non-invasively. Although algorithms have been created to aid in clinical decision making, there is not enough evidence to support their generalization across all populations, therefore, more research still needs to be conducted before they can be fully validated. Clinical reasoning, evaluation and judgment should still be the standard for which physicians make the distinction between these pathologies as they care for their patients.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 88%, Disagree: 3%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

Differentiating between a septic hip and toxic synovitis is a balance between the potential morbidity and complications of an undiagnosed, infected hip and unnecessary invasive procedures when conservative management would have sufficed. Clinically, there is major overlap in the presentations of hip septic arthritis and toxic synovitis, and no single variable or laboratory result can sufficiently distinguish the two [1,2]. In fact, laboratory values can all be within normal limits even when hip septic arthritis is confirmed [3,4]. While toxic synovitis is transient, the natural history of an undiagnosed and untreated septic hip can lead to multiple devastating sequelae, such as cartilage damage, osteomyelitis, osteonecrosis and sepsis [5]. Multiple studies have attempted to identify and simplify the diagnostic procedure in order to better guide clinical decision making and treatment.

Although there is no one differentiating factor that can be statistically quantified between hip septic arthritis patients and those with toxic synovitis, Kocher et al. created a clinical algorithm based on four predictive variables [1,5]. These variables include the inability or refusal to bear weight, history of a fever (defined as an oral temperature >38.5˚C), a serum white blood cell (WBC) count greater than 12,000 cells per cubic millimeter (cells/mm3) and an erythrocyte sedimentation rate (ESR) greater than 40 millimeters per hour (mm/hour) [1]. This was carried out retrospectively and then validated later with a prospective study at the same institution [6]. Their results showed a predictive rate of <0.2% and 2.0% without any predictors and up to 99 and 93% when all four predictors were present, in the retrospective and validation study respectively [1,6].

Similar retrospective studies were also carried out at other institutions and included additional diagnostic variables such as C-reactive protein (CRP) and radiographic findings [5,7,8]. Caird et al. found that CRP was a stronger predictor than ESR and in fact was the second strongest predictor behind oral temperature [5]. However, aside from the validation study performed by Kocher et al. at the same institution, the results of that initial predictive model were not reproducible in all populations to the same 99% predictive rate originally described [4].

Another limitation to the current available data lies in the study designs and the statistical analyses used [9]. A systematic review of the literature found that the patient populations did not differ enough to warrant the variance seen in separate studies [9]. The sample sizes of the studies themselves were called into question and even addressed as a weakness in multiple other studies when analyzing the contrast among the studies [5,8–10].

The variability in evidence shows that currently there is no definitive means of distinguishing hip septic arthritis and toxic synovitis non-invasively. Clinicians must continue to use discerning judgment when assessing patients with potentially infected hips through the use of algorithms, imaging and laboratory studies.

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QUESTION 5: What clinical findings (e.g., fever, erythema, reduced range of motion) are most sensitive and specific for the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: A painful prosthetic joint is the most sensitive, but least specific clinical finding in PJIs. Signs of deep tissue involvement (i.e., sinus tract, purulence, abscess and extensive necrosis) are the most specific signs. It is important to note that clinical findings differ notably based on the type of joint involved (hip or knee), as well as to the timing and presentation of PJIs (i.e., early postoperative, acute hematogenous and chronic).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 97%, Disagree: 1%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

Clinical findings are evident from the first patient encounter and can be immensely helpful in assessing the pretest probability of a diagnosis, as well as the subsequent interpretation of tests ordered. Published work reporting clinical findings in PJIs are retrospective cohort studies including only infected patients with PJIs without a comparative aseptic cohort. Moreover, they report the findings of hips and knees, chronic and acute infections all together. As a consequence, clinical findings currently play a limited role in the established diagnostic guidelines for PJIs.

We conducted a systematic review to evaluate the main clinical findings associated with PJIs and their diagnostic accuracy. Of 1,028 potentially relevant citations, 38 articles (4,467 PJIs) were included in the present review.

Pain

Pain is the most common symptom in acute and chronic PJIs. This finding by itself justifies further evaluation to rule out a PJI, mainly during the first five postoperative years, when the occurrence of aseptic loosening is less frequent. While its frequency and intensity are higher in acute conditions, pain may be the most prevalent or even the only symptom of late infections, especially in cases of low virulence chronic PJIs. In early postoperative PJIs, the clinical features associated with the recovery process from the surgical trauma may mask the manifestation of pain caused by an infectious condition.

Fever

Fevers are a specific, but inconsistent, finding that are markedly influenced by time from surgery. While frequent during acute hematogenous infections (75.5%), the incidence of fever for early postoperative and late chronic infections, is much lower (32.5 and 14.0%, respectively). It should be emphasized that fever, without an actual infectious condition elsewhere in the body, is a common finding during the first five postoperative days, as part of the physiological recovery from a total hip or knee arthroplasty [1].

Periarticular inflammation (i.e., effusion/swelling, warmth and erythema)

Periarticular inflammation findings are specific for PJIs, but should be considered in the context of the particular joint involved (hip or knee) and the timing from surgery. As a superficial joint, the knee is more suitable for the early recognition of inflammatory signs and, or symptoms. Comparing the incidence of periarticular inflammation between infected total knee arthroplasty (TKA) and total hip arthroplasty (THA), Zajons et al. [2] found rates of 50 and 14% for warmth and 75 and 29% for effusions, respectively. It should be noted, however, that the warmth around the knee might remain elevated even in the condition of uneventful recovery after TKA [3]. Time from surgery also has a major impact on these findings; chronic PJIs more frequently present without periarticular inflammation compared to acute PJIs and pain may be the only clue for infection in these patients.

Superficial disturbances (i.e., delayed healing, non-purulent wound drainage and superficial dehiscence)

Superficial disturbances, although sometimes described as signs and symptoms of PJIs, should initially be seen as surgical wound healing disturbances or manifestations of superficial surgical site infections, therefore, not a diagnostic finding, but a risk factor for deep infections. Thus, closer follow-up and early intervention should be performed, as these features may accompany PJIs in up to 44% of cases of confirmed early postoperative infections [4–8].

Deep involvement (i.e., sinus tract, purulence, abscess and extensive necrosis)

Deep involvement presents the highest specificity of all clinical findings associated with PJIs (i.e., specificity between 97% and 100%, positive predictive value of 100% and accuracy of 84.3%). Thus, when present, they justify the condition of major criteria for the diagnosis of PJIs [9].

Joint dysfunction (i.e., stiffness and reduced range of motion)

Joint dysfunctions are underreported and descriptions differ widely. Tande et al. [10] reported a sensitivity of 20.5% (95% confidence interval (CI), 9.3 – 36.5) and a specificity of 99.0% (95% CI, 94.5 – 100.0) in a sample of 39 acute hematogenous PJIs compared with 100 non-infected controls. The incidence of joint dysfunction in chronic PJIs in a study by Jacobs et al. [11] reached 41.7% (25 of 60 PJIs). Tseng et al. [12] found evidence of joint dysfunction in 37.3% (22 of 59 PJIs). Notably these studies did not specify TKA from THA. Interestingly, when comparing 172 THA with 148 TKA PJIs, Zajons et al. [2] found

an incidence of joint dysfunction of 74% (128 of 172) in the knees compared to 85% (126 of 148) in the hips.

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QUESTION 6: Should intraoperative purulence be considered as a definitive sign of a periprosthetic joint infection (PJI)?

RECOMMENDATION: Intraoperative purulence should not be considered a definitive sign of a PJI. The definition of purulence is subjective and is neither a sensitive, nor specific, diagnostic marker of a PJI. A validated, objective definition for purulence due to infection is required to set purulence as a diagnostic criterion for PJIs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 75%, Disagree: 22%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Purulence, defined as the presence of pus, has conventionally been considered a definitive sign of PJI and many studies have used intraoperative purulence as a single criterion to diagnose PJIs [1–4]. The Infectious Diseases Society of America (IDSA) in a Clinical Practice Guidelines for diagnosis and management of PJI, indicates that the presence of purulence without another known etiology surrounding the prosthesis is a definitive evidence of PJI (B-III) [5]. However, considering purulence around the implant as a definitive sign of infection seems to have several drawbacks.

First of all, the determination of purulence is based on the subjective interpretation of the surgeon. Although most surgeons might agree on frank pus, they would have different thresholds for considering cloudy or turbid fluid as purulence. Therefore, the definition of purulence is subjective and assessment and classification of what constitutes purulence are based on surgeons' training, experience and other factors. Failure to use objective criteria to diagnose PJIs has been shown to substantially increase the reported infection rates [6,7].

Secondly, the presence of purulent-appearing or turbid synovial fluid has been reported in both non-infected native and prosthetic joints [8–12]. Turbid, yellowish-white fluid may represent the neutrophil-rich liquid that develops as part of an inflammatory reaction in response to an infection [13], but it may also be seen in non-infectious problems such as crystalline deposition diseases [14,15]. Although contemporary biomaterials are relatively inert, they may still release particles that provoke an inflammatory reaction in some patients [16]. In addition, purulence can exist in patients with failure of metal-on-metal (MoM) bearing surfaces [8–10] or failure due to corrosion at the trunnion of the femoral stem [11], but that does not represent a PJI. Moreover, concomitant infection and failed MoM arthroplasty have also been reported with indistinguishable appearance of the periprosthetic fluid or tissue from non- infected failed MoM implants [17,18].

Thirdly, it was shown that purulence had an acceptable sensitivity of 0.82 and PPV of 0.91 but the specificity and NPV were exceedingly low (0.32 and 0.17, respectively). The sensitivity of purulence was significantly higher in acute hematogenous and late PJIs (0.92 and 0.89, respectively), compared with early postoperative PJIs (0.66) [19], but it is still low to be a definitive sign of PJIs.

Fourth, in the early postoperative period, the synovial fluid is usually blood-contaminated and evaluation of purulence in this time period is very difficult [19].

Fifth, studies showed that there is no correlation between the intensity of systemic inflammatory response and the presence of purulence in the affected joint. Alijanpour et al. [19] showed no correlation between erythrocyte sedimentation rate and C-reactive protein levels and the percentage of synovial neutrophils and the presence of purulence in their series of 467 patients. However, they showed an association between the mean number of synovial neutrophil count, which is concordant with the concept that puru-

lence represents a local inflammatory reaction consisting of a high synovial white blood cell count.

Therefore, in the absence of an objective definition, it is difficult to consider purulence as a simple dichotomous variable. Subjective opinion of the surgeon regarding periprosthetic fluid can vary based on their clinical impression or concerns regarding the consequences of misdiagnosing PJIs. Moreover, PJI has a serious impact on patients' health and quality of life because patients may be subjected to additional surgical procedures and long-term antibiotic treatment. Therefore, surgeons should be cautious in applying subjective criteria for ruling in or ruling out PJIs in suspected patients.

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QUESTION 7: Is aseptic loosening (AL) associated with an undiagnosed periprosthetic joint infections (PJIs)?

RECOMMENDATION: Some percentage of AL is due to culture-negative infection, since up to 10% of culture-negative cases contain bacteria when screened by molecular methods. Whether this correlates to an undiagnosed infection causing AL remains unclear. Understanding this issue is limited by the ability of bacterial culture to function as an effective gold standard for detecting infection. The role of molecular techniques such as next generation sequencing in this setting needs to be explored.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 8%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Loosening is one of the most common indications for total joint arthroplasty revision. Differentiating between PJI and AL is important in determining appropriate treatment. Loosening is considered aseptic when the radiographic or clinical findings associated with loosening are present in the absence of clinical or laboratory evidence of infection. Radiographic determination of loosening has an excellent specificity and positive predictive value, however, a poor sensitivity and negative predicative value, and thus should not be used to exclude loosening [1].

There is the possibility that microorganisms live on or around implants without signs or symptoms of infection, which can lead to AL. Several prospective and retrospective studies have supported that at least a fraction of cases with AL have been associated with higher rates of bacterial growth. The reported prevalence of unexpected positive cultures (UPC) in presumed aseptic revision arthroplasty varies from 5.9 to 23.9% [2–14]. This major variation might be due to small sample size, different culturing protocols (detection of bacteriologic 16S ribosomal RNA by polymerase chain reaction, sonication fluid cultures and conventional techniques of fluid and soft tissue cultures), laboratory contamination rates, as well as the heterogeneity of patients included in each study (i.e., revisions for isolated polyethylene wear, dislocation, fracture and implant loosening) [2,5]. Kempthorne et al. reported a case-control prospective study comparing AL patients (cases) and patients undergoing revision surgery for other causes (control) with a positive culture rate of 15% [2].

Some authors have related early AL to hidden PJIs [3,7,11]. Ribera et al. and Fernandez-Sampedro et al. have observed a correlation between microbiology and prosthesis-age, which supports the possibility of early loosening being caused by hidden PJIs [3,11]. Among the studies reported, there is no consensus about the prognostic impact of UPC. Some authors have shown that even a single positive intraoperative culture has been correlated to prosthetic joint failure, especially with early loosening [11,12]. On the other hand, Portillo et al. have found that the growth of low-virulence organisms in revisions for apparent AL is not associated with early prosthesis failure [8].

While traditional laboratory analysis to evaluate for infection consists of intraoperative culture of periprosthetic tissue or fluids, it has been well-established that microbial culture is an imperfect means of detecting bacteria, as culture has been shown to fail to detect bacteria in as many as 15% of clinically apparent infectious cases [15]. The increasing utilization of molecular methods in recent years has increased the incidence of bacterial detection in cases of AL. One study of 74 culture negative aseptic implants revealed the presence of bacteria in 9 (12%) after screening with polymerase chain reaction (PCR) assays [16].

The discrepancy between traditional culture methods and culture-independent molecular methods to detect bacterial infection in implants has been discussed extensively in the literature [17]. A number of proposed theories have been put forward to explain the absence of cultured bacteria in clinically infected cases, including the effects of prophylactic antibiotic treatment, growth behavior of biofilms and insufficient growth time to detect orthopaedic-specific pathogens. Regardless of the reason, detection via culture appears to be an inadequately sensitive diagnostic tool for periprosthetic joint infections.

A consistent limitation of studies that compare molecular techniques to culture is a failure to perform complete (deoxyribonucleic acid) DNA sequencing. Without this additional information, confirmation and agreement cannot be made between samples that are both culture and PCR-positive. Additionally, the etiology of culture negative and PCR-positive samples cannot be explored. Studies that have conducted full DNA sequencing have found significant discrepancies between the predominant species in culture versus those found via PCR analysis and the classic bacterial species that would be expected in PJIs [16]. The role of contamination in molecular methods also remains ill-defined. A carefully conducted study directly addressing this question found no significant difference in culture and 16S rRNA PCR of explanted implants [18].

An alternative theory to explain the phenomenon of culture-negative and PCR-positive clinically infected cases is the role of endotoxin. The detection limits for endotoxin are comparable to the stimulatory threshold, possibly resulting in unrecognized endotoxin [19]. Endotoxin alone replicates the effect of aseptic loosening [20] and can also adhere to titanium particles and implant surfaces [21]. In cases where bacteria are truly eradicated, cellular debris may create a false positive PCR, and residual endotoxin may initiate a local inflammatory response, resulting in culture negative loosening [22].

It is apparent that advanced modern molecular techniques detect bacteria in aseptic joints at a greater rate and with greater diversity than traditional microbial cultures. It is likely that a PJI is present in a greater number of cases with implant loosening than previously suspected. More detailed studies are required to determine the true incidence of loosening due to infection and the exact pathogenic process that may differentiate culture and PCR-positive infections from culture-negative, but PCR-positive infections.

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QUESTION 8: Can periprosthetic joint infection (PJI) be assigned a high- or low-grade infection? If so, what is the definition of each grade?

RECOMMENDATION: Yes, PJI can be scored and assigned an "infection grade." At this juncture, we recommend using the McPherson schema as a starting point for grading PJIs, as this system demonstrates outcomes correlating with worsening host and limb scores. We suggest this schema (or a modified version) as a starting point until an international workgroup establishes a codified staging system.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 74%, Disagree: 12%, Abstain: 14% (Super Majority, Strong Consensus)

RATIONALE

Infection severity in PJI depends upon multiple factors. These include: infection duration (i.e., acute, acute hematogenous or chronic), the ability for the patient (i.e., host) to combat the infection, the quality of the tissues around the infected joint, the ability for the limb to heal and the "aggressiveness" of the organism.

The duration of infection relates more to the presence of biofilm. Acute infections are essentially non-biofilm-related infections. They characteristically present with abrupt onset and manifest with rapidly increasing pain, displaying overt signs of infection and, not infrequently, developing systemic effects and sometimes even septic shock. Acute PJIs can be successfully treated with early radical debridement surgery. The success of implant retention long-term depends on many factors including early versus late intervention, host comorbidities and local wound health.

In contrast, a chronic PJI involves biofilm formation. This is important because the clinical manifestation of a PJI developed from a biofilm is markedly different from an acute (non-biofilm) infection. In a biofilm-related infection, bacteria and/or fungi adhere to the implant, colonize and expand in size. Once the colony reaches a genetically predetermined size, the colony undergoes a metamorphosis into a biofilm colony (via phenotypic expression). The microbial biofilm then encapsulates the implant system, erodes into the surrounding bone and eventually enters the medullary canals. Furthermore, biofilm colonies are highly resistant to antibiotics, whereby they become 1,500 to 10,000 times more resistant to typical minimum inhibitory concentration (MIC) of antibiotics.

The clinical presentation of a biofilm infection mirrors the progression of the advancing biofilm. This includes gradually increasing pain and periarticular swelling and warmth on examination. Functional limitations result when implant stability is compromised by marginal erosive osteomyelitis. Biofilm bacteria erode into the periarticular soft tissues, creating multiple loculated abscesses destroying vital joint ligaments, tendons and muscle. Not infrequently, a burrowing abscess will erode to the skin surface creating a chronic sinus tract. The time sequence for developing a mature biofilm is variable, but can develop as soon as a few days after the onset of infection in a patient with a joint arthroplasty in place. The rate of biofilm development depends on host immunity and limb health (i.e., local wound health). Characteristically, biofilm infections are considered "indolent" infections, as patients are not systemically ill. This is because endotoxic or exotoxic responses are not manifested with biofilm infections. A biofilm PJI must be treated with implant removal combined with a radical "tumoresque" removal of adjacent soft tissues and bone. This can be accomplished either with a single or two-stage exchange. The choice of single- versus two-stage exchange again hinges upon host and limb health, which can be scored and rated. In the overall totality of PJIs, biofilm PJIs cause vastly more internal damage to the musculoskeletal system than acute infections. Thus, many physicians and surgeons consider a long-standing chronic biofilm infection to be the more severe infection.

The human immune system plays the most critical role as it relates to infection containment and eradication, for both acute and chronic infections. As a general rule, the weaker the human host, the weaker the immune system and, thus, the greater the severity of infection/conditions. There are numerous medical conditions, medications and treatments that can suppress immune system function and alter the course of a PJI [1]. These conditions that have been shown to increase infection risk are well enumerated in the literature over the last four decades.

Grading Schemes

Several schemata for classifying the human host and PJI have been introduced, beginning in the late 1990's. Several authors, including Tsukayama, McPherson, Hanssen and Wimmer, have proposed staging systems for PJIs [2–7]. These have been based on retrospective studies that rate human host quality (i.e., host grade), correlating host grade with worsening outcomes. McPherson et al. has correlated worse outcomes with declining host grade and limb score in both total hip arthroplasties (THAs) and total knee arthroplasties (TKAs) [4,5]. This has been confirmed by Kaplan Meier survival analysis in a recent retrospective review by Bryan et al. [8]. Recently, another study of second-stage THA for chronic infection correlated infection recurrence directly to a compromised host grade [9]. Generally speaking, many infection-specific societies, such as the European Bone and Joint Infection Society (EBJIS), are adopting the staging of host immunity along with limb scores as a means to compare clinical outcomes. In this manner, future treatments for PJIs can be tailored, similar to cancer therapy, based upon an agreed staging system.

Limb tissue health also plays an important factor in infection treatment. Poor tissue health correlates with poor healing and infection persistence. Many factors have been described that limit healing, including arterial and venous insufficiency, sensory and motor neuropathies, soft tissue loss and tissue quality (e.g., irradiation, burns and/or multiple incisions). A poor "limb score" should correlate with reduced outcomes scores, however measured. There are quantifiable parameters with retrospective data supporting this concept. McPherson's schema is thus far the only system that rates limb health and has shown a correlation of impaired limb scores with worsening functional outcomes [4,5,9].

Aggressiveness of an organism is hard to quantify and qualify. The organisms more likely to form a biofilm and persist have multiple techniques to adhere to an implant surface and form a

biofilm. In contrast, organisms that present with acute infections frequently produce toxins that result in a systemic toxicity and eventually shock. Vasso defined a low-grade infection as one that is not causing systemic illness [10]. Symptoms are sometimes ill-defined. Lab serologies may be slightly elevated and cultures can be difficult to grow. When an organism is isolated it is often a low-virulent organism, such as *Staphylococcus epidermidis* or *Cutibacterium acnes* (formerly *Propionibacterium acnes*). In contrast, a high-grade infection has not been as well-established in the literature [11]. One can deduce that it would be caused by an organism causing systemic illness/sepsis or acting aggressively at the site (i.e., severe pain, swelling, drainage, etc.). Currently, there is no method of qualifying these parameters. Medical advancements, such as 3rd and 4th generation deoxyribonucleic acid (DNA) sequencing, will help make it a possibility to identify genetic sequences that correlate with "organism aggressiveness" and poor outcomes. Only then will we be able to truly "rate" the severity of an invading organism.

Conclusions

In summary, there is substantive data that supports the concept of grading or rating a PJI. The data that supports grading PJI severity is retrospective in nature. There is not yet an international codified system that multiple investigators have agreed upon. Our recommendation is to gather an international workgroup to establish a PJI grading system, utilizing current tools and data available. The system of grading should be reviewed and upgraded every five years, as newer diagnostic tools and outcome data become available. For now, the McPherson schema has taken hold and is used in presentations worldwide over the past three to five years. We suggest using this system (or a modified version) as a starting point until an international workgroup establishes a codified staging system upon which the majority agrees.

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2.2. DIAGNOSIS: ALGORITHM

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QUESTION 1: Do you agree with the American Academy of Orthopaedic Surgeons (AAOS) algorithm for the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Yes. However, since the introduction of the AAOS algorithm for diagnosis of PJIs, numerous new tests and diagnostic modalities have become available. The proposed evidence-based and validated algorithm includes the guidelines from AAOS and the 2013 International Consensus Meeting (ICM) on PJIs. A stepwise algorithm first using serological markers followed by more specific and invasive tests continues to be recommended.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 73%, Disagree: 23%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

The guidelines for the diagnosis of PJIs introduced by the AAOS provided useful parameters for clinicians and a framework for diagnosing PJIs [1,2]. These guidelines have been widely adopted and were endorsed at the last ICM on PJIs in 2013 with slight modification [3]. While the existing algorithms are widely accepted, they are not completely evidence-based and have not been validated. Furthermore, several new synovial [4], serum and molecular biomarkers [5–10] have been introduced in recent years, which have increased confusion as many surgeons are unsure how to incorporate these tests into their practice and into the previously established guidelines.

With the introduction of new diagnostic tests and the need for validation of the guidelines, we have been prompted to expand on the prior guidelines and to develop an evidence-based, validated diagnostic algorithm. A multi-institutional study was performed by members of this workgroup, to generate a stepwise approach using random forest and multivariate regression analyses to generate relative weights and to determine which variables should be included

in each step. Ultimately, the algorithm shares many similarities to the previous algorithm as serological testing should be performed first, followed by more invasive tests. This stepwise approach of serological markers prior to joint aspiration has been demonstrated to be the most cost-efficient method of diagnosing PJIs using a multicriteria decision analysis in prior studies [11].

The first step in evaluating for a PJI should include serum testing for C-reactive protein, D-dimer and erythrocyte sedimentation rate. If at least one is elevated, or if there is a high clinical suspicion, clinicians should proceed with synovial fluid testing including a synovial fluid white blood-cell count with differential and leukocyte esterase testing. Intraoperative findings including purulence, histology, next generation sequencing (NGS) or a single positive culture can aid in cases where the diagnosis has not been conclusively ruled in or out prior to revision surgery, or when the aspiration does not yield fluid for analysis (a dry tap). The proposed algorithm was formally validated on a separate cohort of patients and demonstrated a high overall sensitivity (96.9%, 95% confidence interval (CI): 93.8-98.8) and specificity (99.5%, 95% CI: 97.2-100).

In the patient with a painful total joint arthroplasty, it is important to always consider infection. Initially, the first step considers patient risk factors, clinical findings and serum markers; the latter two of which have high sensitivity, but not necessarily high specificity in order to minimize false-negatives. In the multicenter study, approximately 13% of PJIs could be diagnosed with the first step based on a positive sinus tract. It is important to consider clinical suspicion and patient risk factors, (i.e., pretest probability), to optimize sensitivity as serum testing alone is negative in approximately 2.5% of patients who have a PJI [12]. The next step in the investigation of PJIs requires synovial fluid testing which has greater sensitivity and specificity, but is more invasive. The majority of PJIs will be identified following joint aspiration and synovial fluid analysis (approximately 65%). If a diagnosis of PJI cannot be confirmed or excluded at this point, intraoperative findings should be used and approximately 17% of PJIs will be diagnosed after incorporating intraoperative findings including culture, histology, operative appearance and NGS.

It is important to note that it is possible that the diagnosis of PJI may not be made even after reaching the third stage or may be inconclusive after obtaining synovial tests. These patients are often encountered in clinical practice and represent a real diagnostic challenge. Future research and novel tests are certainly needed in this patient population to reduce the gray area in these borderline patients without overt infection. Furthermore, it is important to note that the proposed algorithm and the definition of PJI may be inaccurate and require a modification in the tests utilized for the following conditions: adverse local tissue reactions, crystalline deposition arthropathies, inflammatory arthroplasty flares and infections with slow growing organisms, such as *Cutibacterium acnes* (formerly *Propionibacterium acnes*). Nevertheless, we hope that the introduction of this evidence-based and validated algorithm may simplify a very challenging process and account for recent advancements in the diagnosis of PJIs.

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QUESTION 2: Are there any contraindications to knee or hip aspiration prior to revision surgery?

RECOMMENDATION: There are no clearly identified contraindications to aspiration of the knee or hip joint performed as part of the patient workup for infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 8%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Aspiration of a joint is one of the most important aspects of the workup of a patient suspected of having an infected joint. There are numerous studies that have demonstrated the utility of joint aspiration in aiding diagnosis of periprosthetic joint infections (PJIs). In fact, joint aspiration is one of the initial steps in the workup of a patient for diagnosis of PJI, which is reflected in the algorithm

that is proposed by the International Consensus Meeting (ICM) and presented elsewhere in this document.

The question here is not, however, regarding the utility of joint aspiration in the diagnosis of PJIs, but is regarding possible contraindications for joint aspiration. To our knowledge, there is no publication that specifically addresses this question. In clinical practice, there are a few situations that may compel an orthopaedic surgeon or other physicians to avoid aspiration of the joint. One situation is the presence of cellulitis around a joint that is being investigated, with the concern here being that placing a needle through a potentially infected tissue might transfer bacteria into the deeper space of the joint and result in infection. There are no studies that specifically address issues of cellulitis or skin problems overlying the site of aspiration.

The other situation when physicians may refrain from aspiration of a joint is when the patient is on an anticoagulant. There are several studies that discuss the issue of joint injection or aspiration for patients on concomitant anticoagulation medications. Most of the studies address injections and not aspirations, or have far fewer patients undergoing aspiration than injection. Of the studies that are available, there are several low to moderate quality investigations that discuss patients on anticoagulation during an injection or aspiration. None of these studies have found a statistically significant increase in complications including bleeding or infection related to the procedure.

Yui et al. performed a retrospective review of patients on direct oral anticoagulants (DOACs) undergoing arthrocentesis or joint injection [1]. There were 1,050 procedures reviewed with no major bleeding complications reported. Ahmed et al. conducted a retrospective review of clinical records of patients who were on therapeutic anticoagulation, comparing arthrocentesis or joint injection in patients who had an international normalized ratio (INR) of >2.0 (456 procedures) to those with INR <2.0 (184 procedures) [2]. The authors found only one major bleeding complication and one late infection in the group with an INR > 2.0 and no statistically significant differences between the two groups. It is important to note that many of the patients in both of these studies were also on antiplatelet agents, but subgroup analysis was not performed. Other small, low quality studies have shown no significant risk of complications [3][4]. A recent review of literature of bleeding risks associated with musculoskeletal procedures recommends that anticoagulation agents such as aspirin, clopidogrel, warfarin and low-molecular-weight heparin (LMWH) should not be discontinued in patients undergoing arthrocentesis and/or joint injections [5]. The conclusions of the latter study were based on the review of the available literature. Although high level studies are lacking, there is some support from retrospective studies for performing joint aspiration in patients who are on anticoagulation.

There is no high-level publication regarding the issue of aspirating a joint through skin affected by cellulitis or other skin lesions, such as psoriasis. The available studies are all expert opinions [6]. In the absence of concrete evidence, we feel that joint aspiration performed as part of workup for PJI is a critical diagnostic step and should be performed even in the presence of cellulitis or other skin lesions. Whenever possible, however, the aspiration should be performed through an area that is least affected. Consideration should also be given to postponing the aspiration in patients with stable and chronic issues until any skin lesions have resolved. The decision to proceed with aspiration in patients with skin lesions around the affected joint needs to be individualized and weighed against the theoretical risk of seeding the joint with bacteria from the overlying affected skin.

Another situation that may create issues regarding aspiration of a joint is in patients with bacteremia. It is hypothesized that traumatic arthrocentesis can theoretically introduce infected blood into the sterile joint. There are no human studies related to this subject matter and no studies have specifically evaluated the risk of PJIs in this situation. Olney et al. investigated the risk of performing a joint aspiration in the setting of bacteremia using a rabbit model and found that 30% of animals developed septic arthritis if blood drawn from an animal with bacteremia was injected into the joint [7]. Thus, one can extrapolate that performing a traumatic arthrocentesis in patients with positive blood cultures may potentially result in seeding of the aspirated joint and subsequent infection. This theoretical risk should also be individualized and weighed in the context of benefits versus risks of joint aspiration.

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QUESTION 3: In the setting of a dry tap, should lavage with a fluid be performed?

RECOMMENDATION: We recommend against injection of normal saline or other fluids into a joint that did not yield any synovial fluid (dry tap) and is being investigated for a periprosthetic joint infection (PJI); except in certain circumstances (e.g., a dedicated radiologist performing aspirate in a sterile fashion).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 83%, Disagree: 14%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Joint aspiration is a valuable investigation for the diagnosis of a PJI. In addition to providing information regarding synovial white blood cell (WBC) count, neutrophil differential and biomarkers, it can identify the infecting organism and antibiotic susceptibility [1]. Furthermore, it can guide surgical and antibiotic treatment strategies, such as the choice of appropriate antibiotics for parenteral administration, use of local antibiotics or addition of antibiotics to cement [2]. Aspirated synovial fluid is usually sent for a synovial fluid WBC count, neutrophil differential and processed for isolation of aerobic and anaerobic microorganisms [3]. Given the ability to get these three data points from one intervention, arthrocentesis remains one of the best single maneuvers physicians can perform to rule in or rule out the diagnosis of PJI [4].

A prospective study of 207 revision total hip arthroplasties (THAs) found that hip aspiration had a sensitivity of 0.86 and specificity of 0.94 for diagnosis of PJIs [5]. Moreover, the authors proposed a selective role for aspiration. They concluded that hip aspiration should be limited to confirming clinical suspicion of infection or as an adjuvant investigation when inflammatory markers were falsely elevated secondary to other disorders. Additionally, Barrack et al. performed a retrospective review of 270 hips with routine preoperative hip aspiration, reporting a sensitivity and specificity of 0.50 and 0.88 for the first aspiration, respectively, and a false-positive rate of 13% [6].

However, a dry tap of prosthetic joints is not infrequent and can be disappointing in the setting of an evaluation for PJIs. Historically, injection of sterile saline into the joint followed by re-aspiration has been described as a method to overcome this problem. To date, there are no high-quality studies published supporting the diagnostic value of such a method. Additionally, some studies have suggested the subcutaneous tissue infiltration of local anesthetic and intraarticular injection of contrast media should be avoided. This is due to concerns about potential bactericidal and bacteriostatic properties of local anesthetic and contrast media, respectively [7,8]. This preoperative strategy can also dilute microorganism concentration, be unrepresentative of joint fluid and carries a potentially increased risk of causing an infection in an otherwise aseptic arthroplasty. For these reasons, many investigators recommend against lavage of a prosthetic joint that had a dry tap [1,6,9,10].

A few orthopaedic studies consider lavage of the joint and re-aspiration a valid technique to obtain fluid for samples. The sensitivity of this fluid is comparable to the hip aspirations in which good volumes of fluid were aspirated [11–15].

In a retrospective review, Ali et al. [11] investigated 73 potentially infected THA patients, reporting 82% sensitivity, 91% specificity, 74% positive predictive value (PPV), 94% negative predictive value (NPV) and 89% accuracy of preoperative hip aspiration compared with tissue culture for diagnosis of PJI. Of note, 23 (34%) patients had an initial dry tap and were re-aspirated following saline injection resulting in 83% sensitivity, 82% specificity, 63% PPV and 93% NPV. The authors suggest that using saline lavage is reasonable, with comparable sensitivity, but poorer specificity to standard synovial fluid aspirations [11]. However, given the low number of subjects (73 patients), the conclusions of the latter study have limits and cannot be generalized.

Another retrospective study by Somme et al. [12] investigated the use of lavage to aid in the diagnosis of PJIs in 109 patients scheduled for hip revision. Of the 109 aspirates, 23 were gained using lavage and 10 of these patients were correctly diagnosed with infection, with the remaining 13 patients found to not have an infection. Furthermore, this study used lavage regardless of whether a pre-lavage specimen was obtained in 107 aspirates. No patients with a positive post-lavage specimen had a negative pre-lavage specimen. The authors noted that there is value in using saline lavage in dry taps.

Additional early studies demonstrated inconclusive results with respect to lavage following a dry tap. Roberts et al. [13] utilized saline lavage when encountering a dry tap in the aspiration of patients awaiting revision THA with 38 (49%) dry tap aspirates, 5 of which were shown to be infected at the time of surgery. Of these, three had grown organisms from the saline washings and two were false-negatives. In a retrospective review of 71 THA revisions, Mulcahy et al. [14] used saline lavage in three infected patients with dry taps, however, no organisms were cultured from the saline washings.

More recently, Newman et al. [16] reviewed the WBC count and polymorphonuclear (PMN) percentage in infected and non-infected hips being treated with antibiotic cement spacers, comparing aspiration with or without saline lavage. Aspirations performed without lavage yielded a positive culture in 84% [95% confidence interval (CI), 81%-90%]; but in the saline lavage group, positive cultures were found in 76% (95% CI, 76%-86%). There was no difference in the WBC count or PMN percentage in infected versus non-infected hips when using saline lavage. Therefore, saline lavage was not recommended for the diagnosis of persistent infection in this particular cohort of patients. Moreover, a recently published algorithm-based approach for the diagnosis of PJI does not recommend lavage of the joint with sterile saline in order to obtain samples [1]. In contrast, Partridge et al. [17] performed a retrospective review of 580 hip and knee aspirations and concluded that aspiration with lavage following a dry tap provided accurate diagnostic information and yielded similar sensitivities and specificities to direct aspirations.

Given the paucity of evidence, there appears to be little benefit in attempting lavage of a joint when a dry tap is encountered. Importantly, there appears to be a risk of false-negative results when using this technique. This practice may be best justified if there is a special musculoskeletal imaging specialist who is able to perform the lavage and aspiration with great accuracy. In the absence of such specialist, repeat aspirations or alternative diagnostic methods should be employed in the event of a dry tap. In the absence of consistent evidence, further prospective studies with larger cohorts are required.

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QUESTION 4: In patients with multiple arthroplasties in place who have developed a periprosthetic infection (PJI) of one joint, should other joints be investigated for PJIs also?

RECOMMENDATION: We recommend that when a patient develops a PJI in one joint, the other total joint arthroplasties (TJAs) should be examined clinically and if suspicion for PJI remains, or the patient is immunocompromised, then other joints should be aspirated.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 6%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Up to 45% of patients undergoing primary TJA due to idiopathic osteoarthritis require at least one additional, distant, TJA [1]. Due to increasing numbers of TJAs performed every year and the continuous aging population, patients with multiple arthroplasties are expected to increase. Furthermore, mortality rates after revision for PJIs are estimated to be significantly higher than mortality rates after aseptic revisions [2]. This highlights the importance in determining the infection status of other joints in patients with a PJI.

A frequent concern has always been the presence of distant joint PJIs secondary to possible hematogenous seeding [3–14]. Murray et al. were the first to define metachronous, different joint PJIs [12]. They estimated that the risk of failure of a second, prosthetic joint, already in place, when an initial PJI develops, could be as high as 18%. A limited number of studies have been published evaluating the risk of PJIs in patients with multiple arthroplasties [13–17]. Luessenhop et al. presented a similar incidence of 19% of other joint infections among 145 patients who had more than one joint in place at initial PJI [13]. They also identified rheumatoid arthritis as a risk factor among these patients. Furthermore, in a cohort of 55 patients, Jafari et al. showed a 20% incidence of distant subsequent infection at a mean of two years [14]. They also evaluated that the type of organism of the subsequent infection was found to be the same in 36% of the patients. Abblitt et al., in a more recent study, evaluated 76 patients with multiple joints replaced and estimated the rate of subsequent infection to be lower, at 8.3% [15]. This study also emphasized the role of bacteremia during the first infection in developing a subsequent infection. Haverstock et al. described a 6.3% risk of a subsequent PJI from a total of 206 patients [16]. They identified the same bacteria of the subsequent PJI in only 2.9%. Zeller et al. derived 16 patients with concomitant PJIs, from a cohort of 1,185 with prosthetic hip or knee infections, corresponding to 1.4% of their total PJI population [17].

Studies have been consistent in demonstrating that the risk of developing a PJI in a second prosthetic joint is higher than the base line PJI [12–17]. The estimated risk of second joint PJI ranges from 1.4 to as high as 20%. Rheumatoid arthritis and bacteremia have been identified as possible risk factors for an increased risk of multiple joint infections [13,15]. These published data acknowledge that the other prosthetic joints are at increased risk and raise suspicions whether an ongoing sub-acute infection is present at the time of the initial PJI. However, no study in the literature has evaluated whether at the time of the initial PJI, other arthroplasties should be also investigated.

Nevertheless, investigation of other prosthetic joints should be performed depending on the symptoms of that joint at the time of the other joint PJI. The initial approach should include clinical evaluation. If symptoms are present, initial radiographic evaluation should be performed and in the setting of suspected infection, synovial fluid aspiration should be attempted. Clinical investigation must be undertaken always to identify signs that can raise concern for underlying infection. If aspiration is performed, synovial white blood cell (WBC) count and polymorphonuclear (PMN) % should be requested as they have shown to be highly accurate test modalities [18]. On the contrary, cost-effectiveness of aspirating other joints has also not been investigated; therefore, recommendation in favor or against cannot be made with available data. However, we recommend clinical evaluation of other joints to minimize the risk of failure in the treatment of PJIs.

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QUESTION 5: Are point-of-care (POC) rapid tests for diagnosing periprosthetic joint infections (PJIs) validated and useful?

RECOMMENDATION: Yes, there are several useful POC tests which can be added to the diagnostic workup of PJIs. A number of studies support the usefulness and reliability of the leukocyte esterase (LE) test strip and the alpha-defensin lateral flow test kit. Diagnostic criteria for PJIs should be updated and consider inclusion of these tests.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 73%, Disagree: 21%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

A POC test is defined as a medical diagnostic tool which is used at the time of evaluation of a patient with an immediate result. These are rapid and simple medical tests that can be performed at the bedside. The idea behind a POC test is to provide real-time information upon which the treating physician can act.

After our systematic review, 11 original papers [1–11] and 4 review articles [12–15] assessing the diagnostic value of the LE test strip were included. The pooled data of 2,061 patients extracted from the original papers revealed a sensitivity of 85.7% (95% confidence interval (CI), 65.9 to 90.7%), a specificity of 94.4% (95% CI, 85.3 to 97.7%), a positive predictive value (PPV) of 84.3% (95% CI, 71.5 to 91.7%) and a negative predictive value (NPV) of 94.0% (95% CI, 85.8 to 97.1%).

The first prospective study investigating the utility of the LE strip test in diagnosing PJIs was conducted by Parvizi et al. A total of 108 patients who had painful total knee arthroplasties (TKAs) were investigated and the LE test (with a positive result being ++) had a sensitivity of 80.6% (95% CI, 61.9 to 91.9%), specificity of 100% (95% CI, 94.5 to 100.0%), and PPV of 100% (95% CI, 83.4 to 100.0%). The authors concluded that the LE strip test could be used effectively, by itself or in conjunction with other tests, either as a rapid screening mechanism or for confirmation of a suspected PJI [6].

In a systematic review of Wyatt et al. involving nearly 2,000 patients from five studies, the pooled diagnostic sensitivity and specificity of LE for PJI was 81% (95% CI, 49 to 95%) and 97% (95% CI, 82 to 99%), respectively [15]. Another meta-analysis of eight qualified studies with a total of 1,011 participants showed a higher pooled sensitivity of 90% (95% CI, 76 to 96%) and a similar specificity of 97% (95% CI, 95 to 98%) [14].

The limitation of the LE test is blood contamination interfering with readability of the test result. A recent study confirmed the reliability of the LE strip test by reporting an excellent sensitivity (92.0%) and specificity (93.1%). Furthermore, the latter study confirmed that synovial fluid centrifugation is an effective means of overcoming interference from erythrocytes [5].

After our systematic review, six original papers [16–21] and one review article [22] assessing the diagnostic value of the alpha-defensin lateral-flow test were included. The pooled data of 486 patients showed a sensitivity of 78.5% (95% CI, 64.7 to 94.5%), a specificity of 93.3% (95% CI, 87.0 to 99.6%), a PPV of 87.2% (95% CI, 74.6 to 98.1%) and a NPV of 90.2% (95% CI, 83.7 to 98.2%).

Deirmengian et al. introduced alpha-defensin as a robust synovial biomarker; however, the first studies were published about the laboratory-based enzyme-linked immunosorbent assay (ELISA) test (immuno-assay) [2]. Recent studies showed validated good results of the lateral-flow version of the alpha defensin test being a POC test [16–21]. A level II diagnostic study based on the results of 121 patients revealed a sensitivity and specificity of 97.1 and 96.6%, respectively [17]. The largest series was published by Gehrke et al. as a level I diagnostic study with 195 joints of 191 patients. The overall sensitivity of the alpha-defensin PJI test was 92.1% (95% CI, 83.6 to 97.1%), the specificity was 100% (95% CI, 97.0 to 100%), the PPV was 100% (95% CI, 94.9 to 100%), and the NPV was 95.2% (95% CI, 89.9 to 98.2%). The overall accuracy was 96.9% (95% CI, 93.4 to 98.9%) [18].

In the meta-analysis performed by Suen et al., the pooled sensitivity and specificity of the alpha-defensin lateral flow test was somewhat less appealing, being 77.4% (95% CI, 63.7 to 87.0%) and 91.3% (95% CI, 82.8 to 95.8%), respectively [22]. There is clear evidence that the lateral-flow test has a lower accuracy than the lab-based ELISA immuno-assay [18,22]. The test results may be influenced by metallosis [19] or crystal arthropathy, such as gout [23]. In addition, the

test is somewhat difficult to perform as it involves multiple steps for preparation of the sample.

In a recent meta-analysis about synovial fluid biomarkers alpha-defensin and LE demonstrated high sensitivity for diagnosing PJIs, with alpha-defensin being the best synovial marker. However, other synovial fluid tests like synovial fluid leukocyte count, polymorphonuclear (PMN) %, C-reactive protein (CRP), Interleukein-6 (IL-6) and Interleukin-8 (IL-8) that demonstrate good diagnostic performance can also be used in combination for the diagnosis of PJIs [12]. Molecular diagnostic studies, such as synovial alpha-defensin and LE, may provide rapid, accurate identification of PJIs, even in the setting of concurrent antibiotic administration or systemic inflammatory disease [13].

Additionally, there are a few studies exploring potential technologies which were developed as bed-side tests detecting calprotectin [24,25] or bacterial DNA sequences [26,27] as possible diagnostic tools of the future.

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QUESTION 6: What is the prevalence of culture-negative periprosthetic join infections (CN-PJIs) and what are the diagnostic protocols for further investigating these cases?

RECOMMENDATION: The reported prevalence of CN-PJIs in the hip or knee has ranged from 5-42%. Diagnostic protocols for further investigating these cases include repeat sampling, longer incubation of culture samples, sonication of implants, the use of dithiothreitol (DTT) technology, polymerase chain reaction (PCR) and next generation sequencing (NGS).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 91%, Disagree: 8%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Prosthetic joint arthroplasty is one of the most commonly performed surgical procedures in the field of orthopaedics. Among many complications of prosthetic joint arthroplasty, PJIs are among the most catastrophic [1]. It can develop after 1 to 2% of primary hip arthroplasties and 2 to 3% of primary knee arthroplasties [2,3]. The prevalence of PJIs appears to be on the rise because of numerous reasons, most importantly related to the increasing number of patients receiving arthroplasties. Management of PJIs in general, and CN-PJIs in particular, continues to cause challenges.

The incidence of CN-PJI has been reported to range from 5-42.1% in the literature [4–10]. Klement et al. published a study on patients with PJIs who were diagnosed with the MusculoSkeletal Infection Society (MSIS) major criterion or a combination of MSIS minor criteria, and demonstrated that the incidence of CN-PJI was 0.4% and 45.4%, respectively [11].

CN-PJIs are reported to be associated with older age, smoking, referral from outside institutions, preoperative antibiotic treatment and the presence of postoperative wound drainage [1,4].

Some studies reported that 46% of CN-PJI were caused by fungi, 43% by mycobacteria and 11% by other bacteria such as *Listeria monocytogens*, *Cutbacterium acnes (C. acnes),* Brucella, Coxiella burnetii and others [1].

CN-PJI remains a challenging condition to manage, because of the lack of guidelines or protocols to diagnose and manage these patients in particular with regard to the type of antimicrobials needed for treatment [4]. Because an accurate diagnostic algorithm is not available, most clinicians rely on physical examination, clinical suspicion, laboratory tests and radiological findings to reach the diagnosis of PJI in these cases [1]. Clinical and radiographic evaluations are not always reliable for diagnosing CN-PJI and serum indicators may be inconclusive especially in patients with previous antibiotic administration or those infected with slow-growing organisms. Thus, there has been a growing interest in better diagnostic methods that can isolate the infecting microorganisms associated with implant-related infections.

There are a number of efforts that can be made to improve the yield of culture. Obtaining multiple samples, expeditious transfer of culture samples (especially in blood culture bottles) and prolonged incubation of culture samples are proven to be effective [3,12].

Another strategy to improve isolation of infecting organisms is to subject the retrieved implants to sonication in a sterile fluid. This technique was described a few decades ago and popularized by Trampuz et al. who demonstrated that the culture of sonication fluid had a better yield for isolation of infective organisms of hip and knee PJIs than routine culture [12].

Numerous investigators have described the use of molecular techniques in isolating the infective organism. Perhaps the first molecular technique to be evaluated for isolation of infective organisms in PJI was the polymerase chain reaction (PCR) [13–16]. Tuan et al. continued their efforts to optimize the PCR technology and reported their experience with the use of reverse transcriptase RNA (ribonucleic acid) that aimed to reduce the incidence of false-positive cases [15,16]. Other investigators have shown promising findings with the use of PCR as well. Melendez et al. showed that the PCR accuracy for detecting microorganisms in synovial fluid is 88% and these authors demonstrated that PCR can be used to detect unusual species such as Candida and antibiotic-resistant methicillin-resistant *Staphylococcus aureus* (MRSA) [17]. Bereza et al. was able to isolate bacterial DNA using PCR in 90% of patients [18].

One of the issues related to the use of conventional PCR relates to its extreme sensitivity as it can amplify the DNA of contaminated microorganisms. Because of this issue, PCR has not been used as a first line or a single diagnostic tool in the detection of PJIs [1]. Another issue with the use of conventional PCR is that the type of organisms being sought need to be known to allow for the design of the primer. It is clear that the type of infective organisms is not always known. Thus, a broader approach with the use of multiplex PCR has also been investigated. Jacovides et al. explored the utility of the multiplex PCR using the Ibis Biosciences T5000 biosensor system in a cohort of prospectively collected synovial fluid specimens [19]. In the 23 cases that were considered clinically infected, the PCR panel detected the same pathogen isolated by conventional culture in 17 of 18 cases, and also detected one or more organisms in 4 of the 5 culture-negative cases. In addition, the panel detected organisms in 88% (50 of 57) cases in which revision arthroplasty was performed for a presumed aseptic failure.

Tarabichi et al. first demonstrated the utility of NGS for pathogen detection in PJI with the detection of *Streptococcus canis* in a previously presumed culture-negative case [20]. In a recent report, NGS was demonstrated as a useful adjunct for pathogen detection in 81.8% of culture-negative PJI where intraoperative tissue samples were analyzed [21]. Furthermore, in a series of 86 synovial fluid samples, high concordance with microbiological culture was seen with NGS of synovial fluid alone [22].

Thoendel et al. also showed that metagenomic shotgun sequencing is a powerful tool to identify a wide range of PJI pathogens and may be helpful to diagnose the organism in CN-PJI [23]. Based on their study, metagenomics was able to identify known pathogens in 94.8% of culture-positive PJIs. New potential pathogens were detected in 43.9% (43 of 98) CN-PJIs. Detection of microorganisms in samples from uninfected aseptic failure cases was conversely rare (3.6% of cases).

The analysis of synovial fluid with new biomarkers are currently being studied clinically [3]. The alpha-defensin test shows good results in detecting PJIs [1,3,24,25]. The sensitivity and specificity of the alpha-defensin test is greater than 95% and unlike other biomarkers (i.e., erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), polymorphonuclear (PMN) count) it is not affected by previous antibiotic administration [25–27].

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QUESTION 7: Do patients with adverse local tissue reactions (ALTRs) have a higher incidence of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Yes. Patients with ALTRs appear to have a higher incidence of PJIs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 2%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

The diagnosis of PJI can be extremely challenging in patients with a metal-on-metal (MoM) bearings or modular junction-induced ALTRs. The clinical presentation of ALTR may mimic that of PJI and both serum and serologic markers may be elevated in both conditions. Intraoperative findings may include extensive soft tissue necrosis, macrophage foreign body response, perivascular lymphoid infiltrate and even grossly appearing purulent fluid [1–3]. Preliminary research suggests that MoM wear and corrosion particles may alter the periprosthetic environment, therefore increasing the risk of infection by: 1) impeding the immune system; 2) preventing or accelerating bacterial growth; 3) altering antibiotic resistance and metal resistance mechanisms and 4) providing an ideal milieu for pathogens to proliferate in the necrotic tissues around the joint.

While distinguishing aseptic failure from PJI in a patient with an ALTR can represent a diagnostic challenge, diagnostic cutoffs have been suggested with higher synovial fluid white blood cell cutoffs than chronic PJIs without an ALTR; further, metallic debris can lead to errors in reading the synovial fluid cell count and differential and thus it is recommended to perform a manual cell count in cases of ALTR or metallosis [4]. Despite the vast body of literature investigating both ALTR and PJI following total joint arthroplasty independently, there is a lack of clinical data evaluating the concomitance of these phenomena.

A number of in vitro studies have assessed the effects of metal ion wear production on local soft tissue environment and immune response. Daou et al. noted that increased cobalt concentration in periprosthetic tissue resulted in an inhibitory effect on lymphocyte superoxide production, an impaired leukocyte recovery from acid stress and an improved intra-cellular survival of *Staphylococcus epidermidis* [5]. Akbar et al., likewise noted that high concentrations of cobalt and chromium ions produced an adverse effect on T-lymphocyte function, proliferation and survival [6]. In contrast, Hosman et al. found that high concentrations of cobalt and chromium have bacteriostatic effects as a result of inhibition of biofilm formation and bacterial proliferation [7].

Numerous case reports and small case series have highlighted the issue of concomitant ALTR and PJI [1,8–14]. In one dramatic example, Judd et. al. identified an infection rate of 33% in a series of nine patients revised for ALTR [8]. Two case reports describe concomitant ALTR and infection leading to massive necrosis of bone and soft tissue in a total of four patients, suggesting a possible link between ALTR and severe tissue damage from PJI [9,13].

Registry data from the Mayo Clinic reveals an increased risk of PJI among patients who underwent a primary MoM total total hip arthroplasty (MoM THA). Prieto et al. reported a 5.6% rate of revision for PJI in 124 patients who had undergone MoM THA [15]. While this exceeded the historical incidence of 1.3% and the authors postulate that the increased infection risk may be due to molecular effects of ALTR, they note that a causal relationship cannot be established since histologic evidence was not seen in all cases. Another study from the Mayo Clinic registry similarly noted an increased incidence of PJI requiring re-revision among patients revised for failed hip resurfacing. While not all of these revisions were directly attributed to ALTR, Wyles et al. did note that among eight patients revised for ALTR, two were found to be infected [16].

Multiple studies have identified a high incidence of PJI among patients being revised for ALTR [1,15–18]. However, few of these studies have provided a clear definition of how ALTR was diagnosed, and fewer still have utilized MusculoSkeletal Infection Society (MSIS) criteria to establish the diagnosis of PJI. Donell et al. reported a high rate of early failures in 652 MoM THAs with 90 (13.8%) hips revised over 9 years [1]. In their revision cohort, 9 patients (10%) were noted to have a deep infection. While intraoperative findings consistent with ALTR were described as 'sometimes seen,' no clear link was established between these findings and the cases of PJI.

Efforts to clearly define the features of septic MoM THA failures have contributed greatly to our understanding of the incidence of PJI in patients with ALTR. In a series of 104 MoM THA revisions, Grammatopolous et al. identified seven cases of PJI (6.7%) [19]. All PJI cases were strictly defined by the presence of positive cultures in two separate tissue samples and were noted to also have an ALTR. The use of more stringent criteria than MSIS guidelines led the authors to acknowledge that some cases of PJI could have been missed. The author concluded that the 6.7% incidence noted in their study was very high for presumed aseptic revisions as compared to a rate of 2.7% at their institution for a prior revision series with hard on soft bearings. In contrast, Kwon et al. reported on a cohort of 62 patients revised for ALTR, diagnosed based on clinical and MRI findings. Using MSIS criteria they identified seven cases of PJI (11%) which the authors felt were consistent with the published literature for revision of metal on polyethylene bearings citing prior studies.

There are a few studies that refute a possible link between ALTR and a higher incidence of PJI. Dimitriou et al., Liow et al. and Matharu et al. each reported PJI rates of 2% or less in their cohorts of 178, 102 and 64 ALTR revisions, respectively [20–22]. However, no description of the diagnostic criteria used to identify PJI was provided in any of these studies.

A growing body of both in vitro and clinical evidence suggests that ALTR may foster periprosthetic soft tissue changes that predispose to the development of PJIs. However due to small sample sizes, marked heterogeneity in study design and lack of consistent use of strictly defined diagnostic criteria, the quality of the evidence is currently limited. In conclusion, while conflicting evidence from few case series and some in vitro work make definitive conclusions difficult, the preponderance of the evidence suggests that the incidence of PJI is increased in this patient population.

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QUESTION 8: Should we routinely assess for serum/blood metal ion levels (cobalt (Co) and chromium (Cr)) when working up a patient with a painful total joint arthroplasty?

RECOMMENDATION: There is no data to suggest routine assessment of serum/blood metal ion levels (CoCr) in all patients with painful joint arthroplasty. There may be a rationale for second-line assessment of metal levels in painful metal-on-metal (MoM) total hip arthroplasty (THA), hip resurfacing, modular neck femoral components and in certain metal-on-polyethylene (MoP) THA in which trunnion corrosion is suspected.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 4%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

The reintroduction of MoM hip resurfacing and large head MoM THA had unforeseen complications related to elevated local Co and Cr levels. These levels could be associated with tissue necrosis, osteolysis, late dislocation, and rarely, systemic complications [1-3]. The assessment of metal levels in painful MoM THA, recalled MoM hip resurfacings and symptomatic modular neck THA is well accepted, and usually accompanied by advanced imaging techniques [1-4]. Metal ion levels are consistently higher than baseline following MoM THA or resurfacing, but there is no consensus on a "threshold" metal level for surgical intervention [5]. In fact, Matharu et al. reported better success at diagnosing adverse reactions to MoM THA/resurfacing if implant-specific thresholds are utilized [6]. Patients with MoP or metal-on-ceramic (MoC) hip arthroplasties have significantly lower blood ion concentrations than those with MoM bearings [5]. Rarely, deep infection of a MoM THA could occur concomitantly with tissue necrosis, metallosis and elevated serum metal levels. Typically, metal levels are obtained as a baseline in these cases after initial screening studies are obtained, such as serial radiographs and infection labs (i.e., erthyrocyte sedimentation rate (ESR) and C-reactive protein (CRP)). Certain aspects that may increase the suspicion for elevated metal levels include: CoCr head on a CoCr stem, high offset implants, vertically-oriented MoM cups, bilateral MoM-THA, female gender, increased activity, obesity, dual-modular implants (i.e., head-neck and neck-body junctions) and implants with a poor track record [7,8]. However, a recent case report did find an adverse local tissue reaction (ALTR) in a MoM THA without elevated serum metal levels [9].

Over the past five years, there have been several reports regarding corrosion of the modular metal femoral head-femoral stem trunnion junction [4,10-12]. The clinical picture of ALTR involves some type of hip symptoms (i.e., irritable hip, weakness, swelling, etc.), late dislocation or rarely systemic symptoms. It has been suggested that routine metal levels (i.e., Co and Cr) should be obtained in patients with symptomatic MoP THA. In several small series of patients, the diagnosis of ALTR associated with trunnion corrosion is associated with serum Co levels of >1ppb, with Co levels elevated above chromium levels [11,13]. The ESR and CRP may be elevated in up to 50% of patients with symptomatic trunnion corrosion, causing confusion with the possible diagnosis of infection [10,11]. There is some data that the MoP THA of certain manufacturers may be more likely to develop symptomatic trunnion corrosion [10,11,14,15]. In general, metal level assessments are typically a second or third line element of the painful MoP THA and, at present, due to the cost of these tests and the relatively low incidence of "trunnionosis," routine evaluation of these levels may not be indicated.

There is no data to recommend the routine assessment of metal levels in symptomatic patients with ceramic-on-ceramic THA, ceramic or oxidized zirconium-on-polyethylene THA, any total knee arthroplasty (TKA) or in other orthopaedic implants. Utilization as part of an algorithmic approach to the painful joint is acceptable; however, this should occur after more common causes of THA failure are explored first.

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QUESTION 9: How is a periprosthetic joint infection (PJI) diagnosed in the presence of adverse local tissue reaction (ALTR)?

RECOMMENDATION: The diagnosis of PJI in the presence of an ALTR is challenging as many of the commonly used tests for diagnosis (including the appearance of the surgical site) can be falsely positive. An aggressive approach to preoperative evaluation including an aspiration of the hip joint (sending the fluid for a manual synovial fluid white blood cell (WBC) count, differential and culture) is recommended. Testing the synovial fluid for leukocyte esterase (LE) appears as a feasible, inexpensive and reliable test for the diagnosis of PJIs in ALTRs. There is no supporting evidence for other synovial fluid biomarkers in the diagnosis of PJIs in the presence of ATLRs.

LEVEL OF EVIDENCE

Test	Strength
Clinical and radiological findings	Consensus. There is no supporting evidence for PJI diagnosis in ALTR
Serum markers (ESR and CRP)	Strong
Synovial fluid WBC count, manual and PMNs	Strong
Leukocyte esterase in synovial fluid	Moderate
CRP in synovial fluid	Limited
Other fluid biomarkers (i.e., α-defensin, IL-6, and IL-8)	Consensus: There is no supporting evidence for PJI diagnosis in ALTR

DELEGATE VOTE: Agree: 84%, Disagree: 7%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

ALTRs have become increasingly prevalent secondary to failed metal-on-metal (MoM) bearings and corrosion at the head-neck junction associated with metal-on-polyethylene (MoP) bearings [1,2]. Many of the signs and symptoms of ALTRs mimic PJIs including pain, limited range of motion, swelling around the hip and the appearance of purulent fluid seen intraoperatively or at the time of aspiration [3–5]. Furthermore, many of the commonly used markers for the diagnosis of PJI–including the erythryocyte sedimentation rate (ESR), C-reactive protein (CRP), synovial fluid WBC count with polymorphonuclear leukocyte (PMN) differential and synovial fluid alpha-defensin, have all been reported to have higher than expected rates of false positives in the setting of an ALTR. Hence, the diagnosis of PJI is very challenging in this scenario.

Clinical and radiological findings:

There is no supporting evidence for the accuracy of clinical and radiological (i.e., X-ray, CT and MRI) findings for the diagnosis of PJI in presence of ALTR. Nevertheless, by consensus these must be considered essentials for the initial diagnosis suspicion.

The first report to describe the challenges of diagnosing PJI in the setting of a failed MoM bearing was by Mikhael [4]. They reported two patients with failed MoM total hip arthroplasties (THAs). These two patients presented with pain and elevated serum inflammatory markers both of which mimicked an infectious presentation. Similarly, Cooper et al. described several patients eho had comparable presentations–including purulent appearing synovial fluid intraoperatively [2]. This was one of the first reports of symptomatic ALTR secondary to corrosion at the head-neck junction in a MoP bearing. Subsequently, several reports have noted that the synovial fluid WBC count and differential may be falsely positive in this setting. The authors note the false positives may be secondary to cellular debris causing errors in automated synovial WBC counts and differentials [6–8]. Therefore, in the case of an ALTR, a manual synovial fluid WBC count and differential is recommended [4–6,9].

Yi et al. conducted the largest study specifically focusing on the diagnosis of PJIs in hip revision due to an ALTR [7]. In this retrospective study, 150 consecutive failed THAs were reviewed. This study specifically noted the preoperative serum ESR and CRP and the synovial fluid WBC count and differential. A total of 19 of the patients met MusculoSkeletal Infection Society (MSIS) criteria for PJI. Of the 141 attempted synovial WBC counts, 47 of the samples (33%) had a synovial fluid WBC count that was deemed to be inaccurate or unreliable due to the presence of gross cellular debris, metallic debris, clots or some other abnormality in the specimen. They were able to conclude that automated synovial fluid WBC count was prone to false-positive results and should only be relied on if a manual cell count was performed [7]. In a similar study, Wyles et al. reported on 39 patients, of which four were deemed infected [10]. However, synovial fluid WBC count could not be performed in 33% of their samples due to specimen quality [10]. This led Wyles et al. to suggest that the differential was the best diagnostic test [6,10].

Synovial CRP has been suggested as a simple, cost-effective test for improving the diagnosis of PJI due to several reports finding elevated levels in the synovial fluid [11]. However, the cutoff value of synovial fluid CRP varied in each study: 2.8 mg/L, 3.65 mg/L, 6.6 mg/L, 9.5 mg/L, and 12.2 mg/L [12–14] and further research is needed to determine the utility of this measurement.

Tischler et al. reported on the use of a LE reagent test strip as an adjunct for the rapid diagnosis of PJIs. This study examined 76 patients being revised for a failed MoM bearing or corrosion at a modular junction [15]. Five patients were found to have a deep infection. Unfortunately, 15 of the samples had to be excluded as heavy discoloration of the synovial fluid made interpretation of the reagent strip unreliable, which is a known weakness of this testing modality [15,16]. While the LE strip had reasonable sensitivity (80%) and specificity (93%), the positive predictive value was poor at only

50% [15]. The negative predictive value was found to be 98%, however suggesting the utility of LE as a "rule out" test. Additionally, the LE strip test had the second strongest performance compared to sensitivity of synovial WBC count. Based on these results as well as results from other studies, LE test strips can be a valuable intraoperative test for differentiating PJI from aseptic failures [15,17,18].

Alpha-defensin has been proposed as an accurate test for the diagnosis of PJI due to its high sensitivity and specificity [19–24]. Okroj et al. conducted a multicenter retrospective review of 26 patients who had a diagnosis of ALTR, who had alpha-defensin testing performed [25]. One patient in the study met MSIS criteria for PJI. However, alpha-defensin was positive in 9 of 26 hips, including 8 that were falsely positive (31%). In addition to a positive alpha-defensin, all eight patients were positive on Synovasure. However, five of the eight positive Synovasure results included a warning that they may be falsely positive. Unfortunately, like the synovial fluid WBC count, alpha-defensin is prone to false positive results in the setting of ALTR [25].

Histopathology is often used for the diagnosis of PJI as recommended by the American Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guideline and as part of the MSIS criteria [26]. Grammatopoulos et al. studied 104 failed MoM THAs. They identified seven of the hips to be infected and suggested a standard criteria for the histopathologic diagnosis of PJI of greater than five PMN per high-powered field (PMN/HPF) [27].

Many studies on PJI diagnosis have recently shifted focus to synovial fluid, for it is the site of primary infection. Furthermore, use of synovial fluid to aid in the diagnosis is theoretically more sensitive than serum measurements. Many antimicrobial peptides and inflammatory cytokines have been proposed as synovial biomarkers indicating infection [21]. Among these are CRP, interleukin-1 (IL-1), IL-6, IL-8, IL-17A, interferon-γ, tumor necrosis factor and cathelicidin LL-37. The synovial fluid biomarkers alpha-defensin, IL-6 and IL-8 all demonstrated high sensitivity for diagnosing PJIs and potentially could be applied in combination for the diagnosis of PJIs [13,14,24]. However, studies are sparse and there is no supporting evidence of these biomarkers as tools for the diagnosis of PJI in cases of ALTR.

Given these findings, a more aggressive approach should be used when evaluating patients for PJI in the setting of an ALTR. Specifically, prior to revision surgery, aspiration of the hip joint is recommended to obtain cultures. These results may be incorporated into the evaluation in combination with a manual synovial fluid WBC count and differential. LE reagent strips can also be used as an adjunct to diagnosis, assuming the sample is not contaminated with excessive metal debris or blood rendering the strip unreliable. This approach gives the surgeon a preview of the appearance of the joint at the time of revision.

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2.3. DIAGNOSIS: LABORATORY TESTS

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QUESTION 1: What is an acceptable sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for a diagnostic tool for periprosthetic joint infections (PJIs)?

RECOMMENDATION: The validity of a diagnostic tool is traditionally measured by sensitivity, specificity, PPV and NPV. A perfect diagnostic tool would be able to correctly classify 100% of patients with PJIs as infected and 100% of aseptic patients as non-infected. Without a perfect test available, we are left to balance between sensitivity and specificity; increasing one would reduce the other. To reduce the rates of false positives and negatives it is extremely important to take into account the pretest probability for infection, derived from patient risk factors, clinical examination and any other examinations available at the point of assessment.

Table 1. Variety of diagnostic tools for PJI

Variable	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
Serum testing	98.5%* (96.2-99.6)	100% (97.6-100)	100% (100-100)	97.5% (93.7-99.1)
Synovial fluid testing	100%* (98.3-100)	100% (85.2-100)	100% (100-100)	100% (100-100)
Intraoperative Findings	92.9% (80.5-98.5)	95.8% (78.8-99.9)	97.5% (85.1- 99.6)	88.5% (72.0-95.8)
Overall	96.9% (93.8-98.8)	99.5% (97.2-100)	100% (99.7-100)	96.7% (93.3-98.4)

CI, confidence interval
*Sensitivity for being diagnosed as infected or for moving forward for additional workup.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 79%, Disagree: 10%, Abstain: 11% (Super Majority, Strong Consensus)

RATIONALE

The validity of a diagnostic tool is traditionally measured by sensitivity, sensitivity, PPV and NPV. Validity is the accuracy of a test, or, whether a test measures what it is supposed to measure. A perfect diagnostic tool would be able to correctly classify 100% of patients with PJIs as infected and 100% of aseptic patients as non-infected. Without a perfect test available, we are left to balance between sensitivity and specificity; increasing one would reduce the other. To reduce the rates of false positives and negatives, it is extremely important to take into account the pretest probability for infection [1–3], derived from patient's risk factors, clinical exams and any other exams available at the point of assessment.

When approaching a patient with a failed total joint arthroplasty (TJA), PJI should always be kept in mind. At different points and timing of the investigation, we are willing to accept different sensitivities and specificities. In a recent study, a stepwise approach was used to develop an evidence-based algorithm for diagnosing PJIs. This stepwise approach enables us to maximize sensitivity and specificity for each step based on the timing of the encounter, previous tests available and invasiveness (Table 1).

In the first patient encounter, we typically rely on risk factors, clinical findings and simple serum markers to further guide us. At an early stage we want the tests to be a sensitive as possible, as misdiagnosing an infection as aseptic could lead to devastating outcomes. Interestingly, even if serum testing (as a screening tool) is negative, the risk for PJI is 2.5%. This emphasizes the importance of a pretest probability, patients with a high clinical suspicion based on timing from last surgery (< 2 years), number of surgeries on the joint and positive clinical findings such as erythema, tachycardia and reduced range of motion should be further investigated to increase sensitivity in this stage [4–7].

Synovial fluid aspiration is the next step in the investigation. In recent years numerous markers have been shown to be highly sensitive and specific [8–15]. The fact that patients undergoing synovial fluid testing are already identified as having a high risk for PJIs, the addition of the advantages of more knowledge about synovial fluid analysis garnered in recent years, allows the practitioner to have a very good performance test with high sensitivity (100%) and high specificity (100%). A majority of patients will be diagnosed in this stage.

When a definite diagnosis is not made by this point, intraoperative findings should be used to aid in the diagnosis. Patients not diagnosed as infected or aseptic at this point are usually patients with a dry tap or an overt infection in which the diagnosis is difficult. Thus, this stage holds a relatively low sensitivity and specificity and in 15% of the patients reaching this stage, a diagnosis cannot be made. These patients are often encountered in clinical practice and represent a real diagnostic challenge. Pointing out this unique group of patients promotes awareness in both clinical practice and calls for further research and novel technologies to reduce the number of patients in the gray area in an attempt to improve sensitivity and specificity in these borderline patients.

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QUESTION 2: Does the presence of both an erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) below the periprosthetic joint infection (PJI) thresholds rule out the diagnosis of a PJI?

RECOMMENDATION: Serum ESR and CRP levels below the threshold (as determined by the MusculoSkeletal Infection Society (MSIS) and International Consensus Meeting (ICM)) does not exclude the diagnosis of a PJI. Serum levels of ESR and CRP can be normal in some cases of PJI caused by slow-growing organisms.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The diagnosis of PJI is one of the biggest challenges facing the orthopaedic community. There is no absolute test for diagnosis; hence, for a patient who is suspected to have a PJI, clinicians have to use a combination of tests. The first definition for PJI was developed by the MSIS that was later modified by the ICM on PJI in 2013. Based on this definition, the cutoff for ESR was defined as >30 mm/hr and >10mg/L and for CRP (>100 mg/L for acute PJIs) [1]. According to the diagnostic guidelines of the American Academy of Orthopaedic Surgeons (AAOS), serum ESR and CRP are the first line for screening patients who are suspected for PJI [2]. The document introducing the MSIS criteria for PJI explicitly stated that some of the diagnostic markers including ESR and CRP may be normal in the presence of PJI caused by slow-growing organisms that do not elicit physiological inflammation such as *Cutibacterium acnes (C. Acnes)* [3–5].

McArthur et al. [6] reported a 4% incidence of PJI cases that were seronegative (negative ESR and CRP). Most of the patients in this study who had PJI were infected with slow growing organisms including coagulase negative Staphylococcus, *C. acnes* and Corynebacterium. Three patients in their cohort were infected with virulent organisms; however, all had received antibiotics prior to their diagnostic workup. Nozdo et al. [7] reported that PJI cases with *C. acnes* induced a milder systemic response compared to methicillin-sensitive *Staphyloccous aureus* (MSSA) and that high clinical suspicion and prolonged cultures were essential to diagnose PJI in these patients. In another study by Figa et al. [8], authors showed that *C. acnes* PJIs had below threshold values for ESR and CRP in over half their cohort.

Combined ESR and CRP are also often falsely negative. Johnson et al. [9] reported an 11.1% false negative rate for combined ESR and CRP when the MSIS criteria were considered for diagnosis. Authors concluded that this is due to an insufficient inflammatory response mounted by certain patients with PJI, leading to the muted serological levels. Other studies were in line with this finding: Saleh et al. [10] concluded that combined ESR and CRP increased the specificity at a cost of sensitivity. Shahi et al. [11] reported the sensitivity and specificity of combined ESR and CRP to be 84 and 47%, respectively.

Administration of therapeutic antibiotics prior to diagnostic workups in PJI patients can also be a cause for falsely negative ESR and CRP. This can be an additional source of missed diagnosis of PJIs if only ESR and CRP are utilized for screening, as was shown in a study by Shahi et al. [12].

Diagnosis of acute PJI in the early postoperative period is also a challenge as these markers are usually elevated in this phase. Alijanipour et al. [13] did a retrospective study and investigated the suggested thresholds for serological markers. Authors concluded that a different threshold should be used for evaluating patients in the early postoperative period. In another study by Yi et al. [14],

authors reported that the optimal cutoff for diagnosing PJI in the early postoperative period should be higher than those that are traditionally used and recommended by the MSIS.

In conclusion, although serum ESR and CRP are the first line for screening PJI, a negative test result does not exclude the possibility of infection. Surgeons need to be cognizant of this fact and considering the huge burden of misdiagnosed PJIs, in presence of high clinical suspicion we recommend a comprehensive work up using combination of tests to refute or confirm the possibility of infection.

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QUESTION 3: What is the diagnostic accuracy and threshold of D-dimer in the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Recent literature supports the use of D-dimer as a serological marker for the diagnosis of PJIs. D-dimer has been shown to best perform at a threshold of 850 ng/mL. However, this threshold was determined internally from a cohort in a single institution study. Further studies are needed in order to validate this threshold or establish a more rigorous threshold.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 74%, Disagree: 16%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

Serological markers are typically the first line investigations in patients suspected of having PJIs [1]. Current practice as dictated by the American Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guidelines recommends the collection of blood for the measurement of serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). These tests fall short on multiple accounts. These tests may be falsely elevated in patients with a systemic inflammatory state or some other extra-articular infection [2,3]. Secondly, ESR and CRP may produce a false negative result in patients infected with low virulence organisms such as *Cutibacterium acnes* (*C. acnes*) [4]. Lastly, ESR and CRP may be physiologically elevated in the early postoperative period following the index arthroplasty procedure, making it difficult to interpret in the acute setting [5–7]. In light of these shortcomings, there is a clear need for alternative serological markers.

D-dimer, a fibrin degradation product, is a ubiquitous test that has been used as a screening test in patients with a suspected pulmonary embolism [8–10]. In a study by Shahi et al. [11], a consecutive series of 143 revision arthroplasties undergoing surgery for both septic and aseptic failure had blood drawn preoperatively and sent to the lab for serum measurements of D-dimer, ESR and CRP. Using the MusculoSkeletal Infection Society (MSIS) definition of PJI [12] as a gold standard and a D-dimer threshold of 850 ng/mL, D-dimer demonstrated a sensitivity and specificity of 89% and 93%. ESR and CRP demonstrated sensitivities of 73% and 79%, and specificities of 78% and 80%, respectively. In another study by Lee et al, serial blood draws were performed at baseline, postoperative days one, two, three and weeks two and six. Blood was sent for measurements of serum D-dimer, ESR and CRP [13]. Overall, ESR did not normalize until 6 weeks postoperatively while CRP remained elevated until 2 weeks after surgery. Serum D-dimer levels normalized by postoperative day 2. Thus the advantages of D-dimer are twofold: superior sensitivity and specificity, as well as a rapid decline to baseline levels following surgery, allowing for use in evaluation of a suspected acute PJI.

While it is clear that D-dimer outperformed both ESR and CRP at a threshold of 850 ng/mL, it is important to note that this threshold was calculated internally in order to maximize the

performance of D-dimer in this specific cohort. Larger cohorts are needed to not only further validate D-dimer as a serological marker of PJI, but also to develop a D-dimer threshold that can be used universally. Given its superior diagnostic performance and universal availability in hospitals, we recommend the routine use of D-dimer as part of the battery of serological markers used in evaluating a patient with suspected PJI.

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QUESTION 4: How does the level of leukocyte count and neutrophil percentage in the synovial fluid change with time following total joint arthroplasty?

RECOMMENDATION: The levels of leukocyte count and neutrophil percentage in the synovial fluid drop as one moves further away from the index arthroplasty. The latter is the rationale behind using different thresholds for these parameters in the diagnosis of acute versus chronic periprosthetic joint infections (PJIs).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 4%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

We have recognized that the synovial composition changes as postoperative time increases, which is the reason for separate optimal cut-off values in the diagnosis of acute and chronic PJIs. During the last consensus meeting, the recommended cut-off value for the diagnosis of acute PJI (< 6 weeks from surgery) for synovial white blood cell (WBC) count was > 10,000 cells/μL and > 90% polymorphonuclear cells (PMNs) [1]. Likewise, the synovial fluid cut-off values for a chronic PJI were a WBC count > 3,000 cells/μL and > 80% PMNs [1]. When the optimal cut-off values are adjusted for the span of time after a procedure to differentiate an acute and chronic PJIs, synovial analysis remains a highly reliable diagnostic tool with similar diagnostic accuracy between acute and chronic PJIs.

Although adjustments in the WBC count and percentage of PMNs have improved the diagnostic accuracy for acute and chronic PJI, we have a limited understanding of the change in reliability of synovial analysis on a week-by-week basis. For instance, we do not have a strong understanding whether application of the same threshold two-weeks and six-weeks postoperatively has the same diagnostic reliability. Because we do not have literature to compare the proposed situation specifically, we must qualitatively compare two studies utilizing similar threshold cut-off values at different times postoperatively.

Kim et al. and Bedair et al. each investigated the diagnostic accuracy with similar optimal cut-off values from synovial analysis in the early postoperative period following primary total knee arthroplasty (TKA); however, each utilized differing patient inclusion criteria of three- and six-weeks, respectively [4, 6]. Applying a WBC count threshold of >11,200 cells/μL, Kim et al. had a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 100, 98.9, 65.4, and 100%, respectively [6]. Similarly, a percentage PMN threshold of >88% had a sensitivity, specificity, PPV, and NPV of 100, 65.6, 5.7, and 100%, respectively [6].

When compared to the diagnostic characteristics published by Bedair et al. (Table 1), the two studies demonstrate similar diagnostic accuracy for synovial WBC count and percentage PMNs. Therefore, increasing postoperative timespans appears to have limited influence on the diagnostic accuracy between three- and six-weeks from surgery. However, the same might not hold true for the diagnosis of chronic PJI.

Christensen et al. investigated the effect of increasing time intervals on synovial analysis in TKA patients who underwent aspiration as part of an evaluation for PJI and ultimately were determined not to have a PJI [7]. The authors investigated synovial analysis at ≤45 days, 45 to 90 days, 3 months to 1 year, and 1 to 2 years after surgery. Their data demonstrated synovial WBC count and percentage PMNs normalized between three months and one year after surgery [7]. As a result, it is possible increasing postoperative time intervals could alter the interpretation of synovial analysis in the setting of diagnosing a chronic PJI.

TABLE 1. Synovial cut-off values and associated test characteristics

Variable/Statistical Test	Acute Hip PJI [2]	Chronic Hip PJI [3]	Acute Knee PJI [4]	Chronic Knee PJI [5]
Cut-off Values WBC count (cells/μL); %PMNs	>12,800; >89%	>3,966; >80%	>10,700; >89%	>3000; >80%
Sensitivity (WBC count; %PMNs)	89%; 81%	89.5%; 92.1%	95%; 84%	80.6%; 83.9%
Specificity (WBC count; %PMNs)	100%; 90%	91.2%; 85.8%	91%; 69%	91.2%; 94.9%
Positive Predictive Value (WBC count; %PMNs)	100%; 91%	76.4%; 59.3%	62%; 29%	67.5%; 78.8%
Negative Predictive Value (WBC count; %PMNs)	88%; 79%	97.5%; 98.0%	99%; 97%	95.4%; 96.3%

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QUESTION 5: What is the role of alpha-defensin in the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Measurement of alpha-defensin in synovial fluid is a complement to existing diagnostic tests for PJIs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 82%, Disagree: 14%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Alpha-defensins are antimicrobial peptides released by neutrophils in response to pathogens. They can be measured in synovial fluid and have been proposed as an indicator for PJI. Alpha-defensin use as a PJI diagnostic marker was introduced first by Deirmengian et al. in 2014 [1].

There are two commercially available methods for measuring alpha-defensin in synovial fluid: (1) the enzyme-linked immunosorbent assay-based alpha-defensin immunoassay (Zimmer Biomet, Warsaw, IN, USA), which gives a numeric readout within 24 hours and (2) the alpha-defensin lateral flow test (Zimmer Biomet, Warsaw, IN, USA), which gives a binary readout within minutes. Both assays were developed with the intention of matching the MusculoSkeletal Infection Society (MSIS) criteria as the gold standard for diagnosis of PJI.

The Alpha-defensin Laboratory Test

The alpha-defensin laboratory-based immunoassay measures the alpha-defensin concentration in synovial fluid, providing results relative to a signal/cutoff ratio of one. This form of the assay has been studied at numerous institutions, including The Rothman Institute [1], The Mayo Clinic in Arizona [2], The Cleveland Clinic (Cleveland) [3], the Cleveland Clinic (Florida) [4] and the HELIOS ENDO-Klinik [5]. The following table demonstrates the results of these studies. Both the sensitivity and specificity of the alpha-defensin laboratory test exceed 95% when using the MSIS consensus criteria for PJI as a gold standard.

In addition to individual studies, there have been meta-analyses of the alpha-defensin laboratory test. Lee et al. [6] performed a meta-analysis of the performance of the synovial fluid leukocyte count, polymorphonuclear (PMN) %, C-reactive protein (CRP), alpha-defensin, leukocyte esterase, Interleukin-6 (IL-6), IL-8 and culture in diagnosing PJI. They found the alpha-defensin laboratory test to demonstrate the highest sensitivity (97%) of any individual test for PJI. No other test in this meta-analysis had a sensitivity >90%. In this same study, the alpha-defensin test was found to demonstrate the highest specificity (96%) of any individual test for PJI. A meta-

TABLE 1. Institutions studying the alpha-defensin laboratory-based immunoassay

Institution	N	Gold Standard	Sensitivity	Specificity
Rothman Institute	149	MSIS Criteria	97% (3637)	96% (107/112)
Mayo Clinic Arizona	61	MSIS Criteria	100% (33/33)	95% (83/87)
Cleveland Clinic	111	MSIS Criteria	100% (24/24)	98% (53/54)
HELIOS ENDO-Klinik	156	MSIS Criteria	97% (28/29)	97% (123/127)
Cleveland Clinic Florida	70	MSIS Criteria	97% (34/35)	97% (34/35)
Combined	**547**		**98.1% (95%CI: 95-100%)**	**96.4% (95%CI:94-98%)**

analysis by Yuan et al. [7] found that the alpha-defensin test had a sensitivity of 96% and a specificity of 95%. Similarly, a meta-analysis by Li et al. [8] demonstrated a sensitivity of 98% and a specificity of 97%.

The Alpha-defensin Lateral Flow Test

The alpha-defensin lateral-flow test is a rapid test that can be performed in the operating room. The user must follow the device directions and apply synovial fluid, followed by a waiting period which demonstrated the presence or absence of a line. The presence of a line is indicative of a positive test. Obviously, the results of this device not only depend on the inherent diagnostic characteristics of the test, but also compliance with the directions of use. The literature reporting on the performance of the alpha-defensin lateral flow test is not as consistent or controlled as the literature on the laboratory test. For example, whereas all the major studies reporting on the laboratory test are relatively large and utilize the MSIS criteria as a gold standard, the studies reporting on the lateral flow assay are greatly varied in the number of patients and do not all strictly utilize the MSIS or International Consensus Meeting (ICM) criteria.

Four small studies, each with very few PJIs and very large confidence intervals (CIs), reported on their initial experience with the alpha-defensin lateral flow test. Below is a table summarizing their results. It is important to note that the report by Sigmund et al. [9] was methodologically limited by an absence of availability of the synovial fluid white blood cell (WBC) and PMN % for diagnosis, and also by the inclusion of a very large number of spacer block aspirates. Both Kasparek et al. [10] and Sigmund et al. [9] suggested that the alpha-defensin lateral flow test could be used in place of frozen section histology intraoperatively, given the apparent equivalence between the methods in their studies. However, given the very small numbers and very large confidence intervals in these four studies, it is difficult to draw any significant conclusions.

TABLE 2. Smaller studies reporting on the alpha-defensin laterial flow test

Author	N	PJIs	Gold Standard	Sensitivity (95%CI)	Specificity (95%CI)
Kasparek et al.[10]	40	12	ICM	67% (35-89)	93% (75-99)
Sigmund et al.[9]	50	13	Modified MSIS	69% (46-92)	94% (84-100)
Suda et al.[11]	30	13	MSIS	77% (no range)	82% (no range)
Balato et al.[12]	51	16	ICM	88% (75-95)	97% (87-100)

There are also three large studies of the alpha-defensin lateral flow test that utilize the MSIS criteria as a gold standard. Below are the summarized results of their results in a table format. The report by Renz et al. [13] did include alternative results when compared to other diagnostic criteria, but for the purposes of remaining consistent, only MSIS criteria-based results are included in this Table 3.

TABLE 3. Larger studies reporting on the alpha-defensin laterial flow test

Author	N	PJIs	Gold Standard	Sensitivity (95%CI)	Specificity (95%CI)
Berger et al.[14]	121	34	MSIS	97% (85-100)	97% (90-99)
Gehrke et al.[15]	223	76	MSIS	92% (84-97)	100% (97-100)
Renz et al.[13]	212	45	MSIS	84% (71-94) 94% excluding sinuses	96% (92-99)

There are two studies attempting to use meta-analysis techniques to evaluate the lateral-flow test. One, by Suen et al. [16], does not include the recent large studies by Gehrke et al. [15], Berger et al. [14] or Renz et al. [13]. Furthermore, they included the report by Sigmund et al. [9] which is problematic due to the lack of diagnostic data and inclusion of a very large population of spacer block aspirates. A second study by Eriksson et al. [17], is similarly limited in that recent large studies are not included but includes the potentially limited study by Sigmund et al. [9].

Special Considerations

The alpha-defensin immunoassay test seems not to be influenced by prior administration of antibiotics and covers a wide spectrum of potential pathogens causing PJI [18,19]. Additionally, its results do not appear to be affected by patient-related factors such

the presence of inflammatory diseases [White Paper Synovasure alpha-defensin; CD Diagnostics, Claymont, DE, USA].

Given that the alpha-defensin tests are protein immunoassays, it is critically important that the fluid tested is actually synovial fluid. Aspirates resulting from a saline lavage are not appropriate for any biomarker testing. Furthermore, while blood contamination does not appear to alter the results of the alpha-defensin test, it is critical that the aspirate is actually synovial fluid, and not pure blood from a postoperative hematoma. The following are general precautions when utilizing the alpha-defensin test.

1. Do not request the test when the aspirated sample is from a saline lavage.
2. Pure blood aspirates (e.g., postoperative hematomas) should not be sent for biomarker testing. However, simple blood contamination does not appear to affect the test.
3. Aspirates from prosthetic joints with metallosis demonstrate approximately a 30% false positive alpha-defensin rate.
4. False-negative alpha-defensin results may be observed in the setting of a sinus tract (similar to that observed for the leukocyte count). Fortunately, a joint arthroplasty with a sinus tract is accepted by all criteria for PJI to be deterministic of the diagnosis of PJI. Therefore, a false-negative alpha-defensin result in the setting of a sinus tract should not cause a false diagnosis or be detrimental to patient care.
5. Immediate postoperative aspirates rarely demonstrate mature synovial fluid but are more likely to consist of hematoma. Biomarker assays should not be utilized in the first four to six weeks after surgery.
6. The alpha-defensin test has not been validated for use in the setting of a spacer block.

Summary

Appropriate use of the alpha-defensin test should be exercised. It is not intended to be utilized from aspirates from a saline lavage, gross postoperative hematoma, spacer block or a joint with a sinus tract. Furthermore, the test should be used with proper expectations in the setting of metallosis, as false positive testing appears to be demonstrated at a rate of 30%.

The alpha-defensin laboratory test appears to be the most sensitive and specific single test for PJI and therefore appears suitable to be included in the armamentarium of tests routinely used. Given its combination of a high sensitivity and high specificity as demonstrated in multiple institutions and meta-analysis, it serves well as both a good rule-in and rule-out test and could be given significant weight compared to other individual tests.

The alpha-defensin lateral flow test demonstrates results which appear at least equivalent to frozen section histology, providing for a more rapid and convenient intraoperative solution. Although several smaller studies suggest that the lateral flow test is substantially less sensitive than the laboratory assay, larger studies suggest that the sensitivity is only marginally less sensitive, but remains above 90%. The big advantages of the lateral flow test are that it can be utilized perioperatively and that it gives results within minutes. These features make the lateral flow test useful in ruling-in infection. These results must be carefully interpreted when they show negative results. Although further studies are needed to define the exact sensitivity of the lateral flow test, it appears to be the most accurate rapid test for PJI.

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QUESTION 6: What is the diagnostic accuracy of histologic tests and thresholds used in the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: There is a variability of the histologic examination of intraoperative frozen sections as well as the thresholds used for the presence of neutrophils. The preparation and interpretation of frozen sections can be highly operator-dependent.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 88%, Disagree: 5%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

A recently published meta-analysis of longitudinal studies that compared histologic results with simultaneously obtained microbiologic cultures by Tsaras et al. 2012 [2] included 26 studies, published between 1982 and 2009 and included 3,269 patients who had undergone hip or knee arthroplasty. Of those patients, 796 (24.3%) had a culture-positive PJI. Using the diagnostic criteria chosen by the investigating pathologist, the pooled data showed that a positive result from a frozen section by histopathology predicted a 75% (95% confidence interval (CI), 67-82) probability of a positive culture infection and a negative frozen section result predicted a 5% (95% CI, 4-8) probability of a culture-positive infection. In 15 studies, the threshold of 5 polymorphonuclear leukocytes (PMN) per high power fields (HPF) in each of at least 5 HPF to define a positive frozen section had a diagnostic odds ratio (OR) of 52.6 (95% CI, 23.7 – 116.2), while 6 studied the threshold of 10 PMNs per HPF and had a diagnostic OR of 69.8 (95% CI, 33.6-145). No statistically significant difference between the two thresholds was found. The authors concluded that intraoperative frozen section histologic evaluation was very good at predicting a diagnosis of culture-positive PJI and had a moderate accuracy in ruling out the diagnosis of PJI.

Corresponding results of a meta-analysis of the accuracy10 vs. 5 PMNs as a threshold in frozen sections to diagnose PJIs was published by Zhao et al. in 2013 [3]. The meta-analysis includes 12 studies, published between 1972 and 2012, involving 1,011 patients undergoing hip arthroplasty of which 194 (19.2%) patients had a PJI. In 7 studies, the threshold of 5 PMNs per HPF was used, in 2 studies, the threshold of 10 PMNs per high-power field was used, while in 3 studies, both thresholds were used. The diagnostic OR was 23.5 (95% CI, 10.5 – 52.7) when 5 PMNs per HPF was used and 35 (95% CI, 7.7– 159.3), when 10 PMNs per HPF was used. Equally, they found no statistically significant difference between the two thresholds. The authors concluded that their results indicates that though both thresholds are stable and effective, a threshold of 10 PMNs per HPF is better for diagnosing PJI.

Since the meta-analysis included studies until 2009 [2], 17 studies [4–20] have been published from 2010 to 2017 and considered as relevant to the question about the accuracy of the method. These studies show a variability of the accuracy between 65.6 and 99%, a sensitivity between 38.8 and 96.6% and a specificity between 77 and 100% [4–20]. The studies were performed at single centers, and the majority of the studies included less than 100 patients of which less than 25 patients were infected.

The accuracy value of thresholds in the meta-analysis by Zhao et al. in 2013 [3] was 85.2% (95% C,I 79.3-91.1) when 5 PMNs per HPF was used and 89.1 (95% CI, 80.5– 97.7), when 10 PMNs per HPF was used. The true positive rate (sensitivity) was 0.67 (95% CI, 0.49-0.86) and 0.6 (95% CI, 0.27-0.93) for 5 PMNs per HPF and 10 PMNs HPF, respectively. The corresponding figures for the true negative rate (specificity) was 0.9 (95% CI, 0.85-0.96) and 0.93 (95% CI, 0.85-1.0).

The results of the meta-analysis [2,3] of the thresholds show wide 95% CI in the diagnostic OR for the 5 and 10 PMNs per HPF, respectively. This may indicate small sample sizes that may not be able to show a difference that exists.

Nevertheless, adequate published evidence exists to support diagnostic thresholds of either 5 PMN in each of 5, 40X HPF (maximum tissue concentration) or 10 PMN in each of 5 HPF to help diagnose or rule-out periprosthetic infection at revision arthroplasty. Exceptions exist, but in general, increasing the concentration of PMN required for diagnosing infection from 5 to 10 PMN per HPF may slightly increase specificity but have little effect on sensitivity. A few studies have advocated using lower PMN concentrations to maximize sensitivity [13,19]. The studies reviewed apply only to tissue obtained at revision arthroplasty of the hip or knee; different optimum thresholds may exist for the shoulder or other sites.

Kashima and his co-workers [21] found that all cases of aseptic loosening contained fewer than 2 PMNs per HPF and that in some cases of septic loosening, fewer than, on average, 5 PMNs per HPF are present in periprosthetic tissues. The study included 76 patients of which 22 were infected. The histological criterion of more than 2 PMNs per HPF showed increased sensitivity and accuracy for the diagnosis of septic loosening. The sensitivity, specificity, and accuracy for +++ neutrophil polymorph infiltration was 83, 96 and 91 %, respectively, and for >++ neutrophil polymorphs 94, 96 and 97 %, respectively. In their conclusion, they suggest that the MusculoSkeletal Infection Society (MSIS) histological criterion of more than 5 PMNs per HPF is too high an index figure for the diagnosis of all cases of hip and knee arthroplasty infection.

Limitations

It is likely that the method of tissue sampling by the surgeon and the experience of the pathologist influence the value of frozen sections obtained at revision arthroplasty. For example, it has been suggested that PMNs entrapped in superficial fibrin or migrating from capillaries in granulation tissue should not be included in the PMN quantification. Pathologists should also avoid misinterpreting granulocyte precursors in the hematopoietic bone marrow that often accompanies these biopsies as suggestive of infection and it can be difficult to distinguish eosinophils from neutrophils in some frozen sections. The microscopic fields selected for PMN quantification should represent the maximum neutrophil concentration, not the overall average on the microscope slide, and tissue obtained from near a recent periprosthetic fracture may contain neutrophils unrelated to infection. Many of the reports in this review fail to specify the above limitations, so subtle differences in the routine practice of pathologists in different centers may contribute to the variable quality of frozen section (FS) interpretation [22]. In addition, the reference standard against which FS interpretation has been meas-

ured has not been consistent. Some authors have considered one positive culture as indicating infection, others have required additional factors or have used the MSIS criteria [7] Other studies have recognized that long-term clinical follow-up may be needed to define clinically relevant periprosthetic infections, especially those involving organisms of low-virulence [23].

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QUESTION 7: What is the role of specific granulocyte counting methods and new immunohistologic staining techniques in diagnosing periprosthetic joint infection (PJI)?

RECOMMENDATION: The role of specific granulocyte counting methods and new immunohistologic staining techniques is to support the diagnosis of infection when diagnosis is uncertain. The recommended threshold is 5 or more polymorphonuclear leukocytes (PMNs) per field in each of 5 high power (400x objective) magnification fields. The stains reported-to-date can only be performed on sections of formalin-fixed, paraffin embedded tissue. Therefore, they are not available for use on frozen sections obtained during an operation.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 85%, Disagree: 4%, Abstain: 11% (Super Majority, Strong Consensus)

RATIONALE

Currently, histology has been considered as one of the variables for PJI diagnosis [1]. Literature has reported on tissue reaction associated with implant failure and its relationship with infection [2]. It has been seen that an increase of PMNs correlates with the presence of an active infection [3,4]. New methods have been introduced to increase diagnostic performance. A literature search of PubMed, Ovid, Embase and the Cochrane Library was performed to include studies that evaluated the role of granulocyte counting methods and/or evaluating new immunohistologic staining techniques. The following types of studies were excluded:

1. Studies with histology metrics were used as the gold standard to test the results of other tests.
2. Studies involving primarily sites other than hip or knee (for example, shoulder operations are excluded).
3. Reviewed articles and case reports.
4. Articles published in languages other than English.

5. Articles with only limited data available such that one cannot calculate the sensitivity, specificity or predictive value of histology.
6. Studies which analyze different aspects of inflammation and therefore have no focus on the diagnostic quantification of granulocytes.

For each, it was attempted to define the results of histology and the influence of special or immunohistochemical stains with respect to true positives, false positives, true negatives and false negatives to calculate sensitivity, specificity, predictive value and accuracy. If that data was unavailable, the values reported by the authors were recorded. The threshold used for interpreting histology as favoring infection, the reference standard and other clinical metrics were also recorded.

Results

The initial search yielded 287 articles, 41 of which were automatically excluded as duplicates. The titles and abstracts of the remaining 246 articles were reviewed and 233 excluded. The remaining 13 articles, reviewed in their entirety, and 9 publications for excluded for the following reasons: 3 were not in English, 3 related to aseptic loosening (not infection), 1 did not involve the use of special stains and 2 had an inappropriate study design. The remaining three [5–7] studies were included in our review:

1. Kashima TG, Inagaki Y, Grammatopoulos G, Athanasou NA. Use of chloroacetate esterase staining for the histological diagnosis of prosthetic joint infection. Virchows Arch. 2015;466:595–601. doi:10.1007/s00428-015-1722-y.
2. Krenn VT, Liebisch M, Kölbel B, Renz N, Gehrke T, Huber M, et al. CD15 focus score: Infection diagnosis and stratification into low-virulence and high-virulence microbial pathogens in periprosthetic joint infection. Pathol Res Pract. 2017;213:541–547. doi:10.1016/j.prp.2017.01.002.
3. Munemoto M, Inagaki Y, Tanaka Y, Grammatopoulos G, Athanasou NA. Quantification of neutrophil polymorphs in infected and noninfected second-stage revision hip arthroplasties. Hip Int. 2016;26:327–330. doi:10.5301/hipint.5000365.

Based on the review of the literature, it is recommended that neutrophil counting methods be included when diagnosis is uncertain. In general, we recommend that 5 or more PMNs per field in each of 5 high power (400 X objective) magnification fields be used as the threshold to support the diagnosis of infection. Additional studies are needed to determine the optimum use of special stains. Although the literature supports the use of special stains for neutrophils to increase sensitivity, the stains reported to date can only be performed on sections of formalin-fixed, paraffin embedded tissue. Therefore, these stains are not available for use on frozen sections obtained during an operation. There is some evidence that findings derived from special stains can also correlate with the virulence of the pathogens involved in the infection.

The above recommendations are based on the review of three studies, one of which is high quality. Based on the range of sensitivity and specificity, the strength of the 5 PMNs threshold is strong, while the advocacy of special stains on permanent sections is moderate.

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2.4. DIAGNOSIS: PATHOGEN ISOLATION, CUTURE RELATED

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QUESTION 1: Should intraoperative cultures be taken during every revision total joint arthroplasty (RTJA)? If so, how many?

RECOMMENDATION: Yes, routine cultures should be taken during every RTJA. At least three intraoperative culture samples should be obtained.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 87%, Disagree: 12%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Using the following search terms and words (revision and joint infection; joint arthroplasty; aseptic loosening and culture), a total of 1,772 results were generated from PubMed, Ovid and Google Scholar. Sixty-five studies were found to have met the inclusion criteria. Publications that did not relate to the topic, case reports and those describing technical details of revision arthroplasty were all excluded. Furthermore, registry studies, articles with inadequate description of tissue sample methodology and studies with few patient numbers were

TABLE 1. Statistical analysis by minimum number of cultures sent per revision TJA (RTJA)

Minimum Number Cultures Sent (Mean)	Total Number of RTJA, n (# of Studies)	Sensitivity, % (Lower-Upper CI)	Specificity, % (Lower-Upper CI)	PPV, % (Lower-Upper CI)	NPV, % (Lower-Upper CI)
<3	2,038 (9)	72 (63-81)	94 (90-98)	80 (58-102)	79 (69-89)
≥3	2,283 (14)	62 (50-74)	93 (88-98)	78 (66-90)	85 (78-92)
Overall	4,321 (23)	66 (58-75)	94 (90-97)	78 (67-89)	83 (77-89)

also excluded. To ensure an acceptable strong to moderate strength body of literature evidence – only prospective, comparative and large retrospective studies were included. The literature search did not yield any randomized controlled trials. Across the studies which met the criteria, two that stated multiple tissue samples were taken and were recorded as at least two samples (due to lack of clarity on the number). In order to determine the optimal number of culture samples to be obtained intraoperatively, we included only studies with revision hip and knee arthroplasty that documented the total number of cultures taken at time of surgery and the corresponding diagnostic accuracy (sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)). The studies were then stratified according to the number of samples sent. Exclusion criteria were studies that did not include all four values of sensitivity, specificity, PPV and NPV. The number of cultures obtained and sent were reported as the mean of the minimum number of cultures sent, as reported in the studies. A meta-analysis was performed to obtain pooled estimates for specificity, sensitivity, PPV and NPV using exact likelihood methods normal-binomial model with empirical ("sandwich") variance estimator. Separate estimates were obtained for studies reporting < 3 cultures and those reporting ≥ 3 cultures.

The reviewed literature revealed that the mean number of culture samples taken across cohorts included in the studies was four (minimum two, maximum eight). There were 23 studies with a total of 4,321 patients undergoing revision hip and knee arthroplasty that documented the total number of cultures taken at time of surgery and the corresponding diagnostic accuracy (sensitivity, specificity, PPV and NPV). The analysis indicated that taking three or more intraoperative samples yielded higher negative predictive value to rule out infection without limiting the positive predictive value to confirm infection (Table 1). It is a known fact that periprosthetic joint infection (PJI) may be present in patients undergoing revision hip and knee surgery for aseptic etiologies, even when preoperative workup suggests that this might be the case. A varying degree of clinically relevant PJI has been associated with presumed aseptic loosening [1,2]. These cases were diagnosed from intraoperative cultures. It is for this reason that we suggest that intraoperative samples be sent for all revision hip and knee arthroplasties, irrespective of preoperative diagnosis.

Up to 12% of cases of total knee and hip arthroplasty (TKA and THA) are revised within ten years. Cases are revised for a variety of reasons, and making a preoperative diagnosis may be challenging [1]. PJI is one of the most morbid complications after total hip and knee arthroplasty. According to the Swedish Hip Arthroplasty Register between 2000 and 2013 the risk of PJI increased from 7.5-13.5%. In patients undergoing revision for an aseptic diagnosis after TKA and THA, 7.9 and 12.1%, respectively, had PJIs [2]. As no gold standard exits for the diagnosis of PJI, clinicians often must rely on a combination of tests to confirm or rule out a diagnosis [3]. There is also a paucity of available standards on how many intraoperative cultures should be taken. Attempts to standardize these practices have been published in the form of treatment guidelines, yet the approach still varies between practitioners and locations. This is in part owing to a paucity of strong evidence to support specific guidelines [4].

Atkins et al. had recommended that five or six intraoperative specimens be sent and that the cutoff for a definite diagnosis of PJI be three or more operative specimens positive for an indistinguishable organism due to the low sensitivity of cultures [5]. Some studies reported on their results when taking five to six intraoperative tissue samples from multiple areas of the infected prosthesis and hip joint including the capsule, pericapsular tissue and membrane around prosthesis. However, some other studies were carried out using a protocol where two to three tissue samples were taken intraoperatively for microbiology culture analysis [2,6–8]. Our present review of the literature shows an average of four tissue samples being taken across the studies which we examined. This is consistent with 25% of the cohort of studies assessed in this review.

There are obvious discrepancies and variations in the protocols and guidelines being adhered to which may vary according to institution. If patients with PJI can be accurately identified preoperatively or intraoperatively, a better outcome might be achieved from revision surgery. Although a combination of preoperative investigations can point towards infection, no test has yet proved to be completely accurate as a stand-alone test [9]. Therefore due to low sensitivity of intraoperative cultures [10], it is only imperative that definite guidelines on how many samples to be taken should be anchored on evidence based literature. In the current body of published studies, there are no randomized controlled studies answering this specific question.

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QUESTION 2: Are there significant differences in the yield of culture between preoperative aspiration and intraoperative culture samples? If so, which result should be utilized?

RECOMMENDATION: There may be differences in the yield of culture between preoperative aspiration and intraoperative culture samples, particularly in the case of polymicrobial infections or low-virulence organisms. The collection of multiple intraoperative tissue samples is considered by many experts to provide the highest yield in isolating organisms from a joint.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

When interpreting culture results in general, one should be aware that the literature demonstrates a lack of reproducibility, whether from the synovial fluid or from the tissue.

Due to inherent methodologic difficulties and limitations in the existing literature and variation in culture techniques between institutions, it is not possible to make a general statement regarding the relative yields of synovial fluid and tissue culture. In general, we recommend that synovial fluid and tissue samples both be sent for culture, as the growth of an organism from either source is highly informative. However, clinicians should be aware that in general, culture techniques have a relatively poor sensitivity for periprosthetic joint infections (PJIs) (40 to 85%), and that negative culture results do not rule out PJI. The current literature does not provide evidence-based guidance on how to interpret contradictory synovial fluid versus tissue culture results. Considerable research is needed to optimize and standardize culture techniques to provide improved yield for isolation of infective organisms.

There are inherent methodologic difficulties in studying the comparative yield between synovial fluid and tissue culture results. First is the fact that while synovial fluid is usually sent to the lab for a single culture, intraoperative tissue samples are usually sent in multiples. Whenever a diagnostic test is completed multiple times and the results are interpreted in combination, the sensitivity increases and the specificity decreases by definition. Therefore, even if the sensitivity and specificity of synovial fluid and tissue culture were identical, the multiplicity of testing associated with tissue culture sampling would result in the observation that intraoperative culture has a higher yield. Tissue samples have a greater opportunity to yield a positive result, whether real or due to contamination.

Second, is the fact that there are no universal standards in arthroplasty culture technique. The collection, transport, sample preparation, culture media and culture times vary greatly between institutions [1-18]. The techniques may even vary based on whether the sample is a fluid or a tissue sample at the same institution. Therefore, the results published at one institution regarding the yield of synovial fluid culture or tissue culture cannot be assumed to apply to all institutions.

Third, is the fact that the definition of PJI has varied over time and had great variability before the MusculoSkeletal Infection Society (MSIS) definition. Many historical studies considered positive tissue cultures to be the gold standard for infection, eliminating the possibility of properly assessing the diagnostic characteristics of tissue culture. Furthermore, different centers have different definitions of what qualifies as a positive tissue culture, with variation in the number of positive samples requirements, the virulence of the organisms yielded and the assessment of broth-only results.

Microorganisms involved in infection of orthopaedic devices are highly adapted on the implant or in the bone-cement interphase, adhering to the environment within the in vivo biofilm, but are only to a minor part in a planktonic state in the synovial fluid [19]. This fact can explain the high rates of preoperative aspiration with false negative bacteriology [11]. Moreover, other factors such as bacterial load or the type of germ may affect synovial culture, which may explain the higher sensitivity of aspiration fluid culture observed in acute versus chronic infections [20, 21]. Although a recent study from Shanmugasundaram et al. could not show any influence of microbial virulence on organism isolation from preoperative aspiration versus intraoperative culture [14], some studies showed insufficient accuracy of synovial fluid culture in isolating low virulent pathogens in chronic PJI compared to intraoperative tissue culture [11, 21].

For the aforementioned reasons, a comparison of the yield of synovial fluid versus tissue cultures cannot be made with any confidence. There are exceedingly few studies comparing the culture sensitivity of synovial fluid versus tissue [1-18]. Of these reports in the literature, there are very significant limitations which prevent the appropriate comparison of synovial fluid versus tissue culture yield. Many of these studies have fewer than 10 patients with PJI. The diagnosis of PJI varies greatly in these studies. And many of these studies fail to provide the proper data in evaluating their analysis and conclusions. Studies seeking to compare synovial aspiration and intraoperative tissue culture results have shown a wide range of concordance (57-92%) [1-18] in the sense of false-negative, false-positive, true-negative and true-positive results. Among these 18 studies, nine were retrospective and nine collected their data prospectively.

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QUESTION 3: Do bone cultures provide additional diagnostic accuracy in the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Inconclusive. We cannot recommend for or against bone biopsy to provide additional diagnostic accuracy in the diagnosis of PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 5%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Use of traditional culture remains the preferred method for isolation of the infecting organism(s) in PJIs. It is reasonable to assume that increasing the number of samples and taking culture from "representative areas of infection" enhances the yield of culture in isolating the infective organism. Current data supports obtaining synovial fluid and tissue samples for culture, with studies showing tissue to have a better yield than synovial fluid and is preferred over swabs [1,2]. Whether the tissue culture should include bone also has not been well studied. In general, multiple samples improve diagnostic accuracy [3]. Most data supports obtaining at least three distinct and as many as six intraoperative samples for culture [2,4]. The site of specimen retrieval includes the synovium, as well as tissue from the femur and tibia in the knee or the femur and the acetabulum in the hip. In addition to traditional cultures, sonication of implants has been shown to possibly increase chance of identifying the organism [5-7].

Only one study addresses the role of utilizing bone biopsy in the detection of infection in joint arthroplasty. In a prospective cohort study, Larsen et al. [8] assess the contribution of different specimen types in detecting PJI. It was found that bone biopsy did not provide any additional information and did not contribute independently to the diagnosis of infection. The bone biopsy was obtained from bone in contact with the prosthesis. Only 9 of 32 samples (28%) resulted in a positive culture after 6 days. This increased to 13 of 32 at 14 days. This was considerably less than soft tissue biopsies which resulted in 37 of 42 (88%) positive cultures. There were no cases where bone biopsy yielded a positive culture independent of soft tissue biopsy. This resulted in a negative likelihood ratio of 0.6 (95% confidence interval (CI), 0.5-0.8) which only slightly decreases the probability of infection with a negative result. This study found the optimal specimen set for diagnosis of periprosthetic joint infection included joint fluid, prosthetic component and five soft tissue biopsies [8].

Other studies have assessed the role of bone biopsy in detecting osteomyelitis and septic arthritis. Bone biopsy in osteomyelitis was found to have significantly improved sensitivity, specificity and predictive value in determining the etiological organism when compared to sinus tract biopsy [9] and soft-tissue and deep wound biopsy [10]. In the setting of septic arthritis, sampling of the ileum

and proximal femur resulted in significantly increased positive culture rates when compared to aspiration of synovial fluid alone [11]. However, it is difficult to extrapolate these findings to assume that obtaining a bone sample in a patient with PJI is likely to increase the yield of culture. In the absence of adequate data, we have refrained from recommending that bone samples for culture should be taken routinely in patients with PJIs.

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QUESTION 4: Is there a role for obtaining cultures before, and at the time of, insertion of prosthesis during second stage (reimplantation) of a two-stage exchange arthroplasty?

RECOMMENDATION: Preoperative aspiration of a joint should be determined based on the index of suspicion for persistent infection. During reimplantation, however, multiple fluid and tissue samples should be sent for culture. There is a direct correlation between the outcome of two-stage exchange arthroplasty and culture results during reimplantation.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 4%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Two-stage exchange arthroplasty consists of removal of the infected prosthesis in the first stage, usually replacing it by an antibiotic-loaded cement spacer and treatment with systemic antibiotics. Once the infection is thought to be under control, the second-stage of reimplantation is performed. The metrics that determine the optimal timing of reimplantation are not known. However, many surgeons rely on a combination of metrics that may include aspiration of the joint prior to reimplantation. The exact role of preoperative joint aspiration prior to reimplantation remains undefined. Furthermore, there is also no specific test to determine if the infection has or has not been controlled.

Although aspiration of a joint is critical for the diagnosis of periprosthetic joint infections (PJIs) [1], it is not obvious if culture of synovial fluid with a polymethyl methacrylate (PMMA) spacer in place before reimplantation is helpful for the diagnosis of persistent infection [2]. In fact, it has been demonstrated that aspiration for microbial culture before the second stage has a low sensitivity for predicting infection [3–6]. Lonner et al. investigated the role of knee aspiration for detection of persistent infection before reimplantation and after cessation of a four- to eight- week course of antibiotics. They found that knee aspiration performed after resection arthroplasty had a sensitivity of zero, a positive predictive value (PPV) of zero, a negative predictive value (NPV) of 75% and a specificity of 92% [6]. Janz et al. studied the diagnostic performance of synovial aspiration in resected hips without a PMMA spacer, for detection of infection persistence prior to total hip arthroplasty (THA) reimplantation. They found a sensitivity of only 13% and specificity of 98% and concluded that aspiration of a resected hip neither reliably confirmed nor excluded the persistence of infection [5]. Hoell et al. investigated 115 patients with two-stage hip or knee arthroplasty and found that the sensitivity of the aspiration culture before replantation was 5% (95 % confidence interval (CI), 0.13–24.87) and the specificity was 99% (95 % CI, 94.27–99.97). The NPV was 83% and the PPV was 50 % [4]. Preininger et al. investigated the diagnostic validity of synovial PMMA spacer aspiration after two weeks of antibiotic holiday for detection of persistent infection. They included 73 patients who underwent two-stage revision for infection and found only 21% sensitivity for synovial PMMA space aspiration. They concluded that synovial PMMA aspiration cannot be recommended for exclusion of persistent infection [7].

There are some potential explanations for this finding. First of all, it is possible for bacteria to be in a biofilm and remain adherent to cement spacer, which in turn leads to uncertain predictability of culture from aspirations before reimplantation [8–10]. Secondly, the

elution of antibiotics from PMMA into the joint may interfere with isolation of the infecting organism from the joint aspirate. Although major elution of antibiotics from PMMA cement spacer occurs early, there is usually adequate elution of antibiotics at later dates that can interfere with isolation of the infective organism [11,12].

Another controversial aspect of two-stage revision for infection is the role of reimplantation microbiology [13,14]. Hart et al. reviewed 48 patients underwent two-stage revision for infected total knee arthroplasty (TKA). They found 11 (22.9%) positive cultures at the time of reimplantation; seven of them were different from the primary infecting microorganisms. They could not find any relation between the positive reimplantation culture and the outcome [15]. Bejoen et al. review 152 patients with PJI who underwent two-stage revision over a 4-year period. Patients were managed with antibiotic free interval before reimplantation. They found that reimplantaion microbiology was positive in 21 cases (14%) but did not correlate with eventual outcome. The same organism, determined by comparing species and antibiotic susceptibility patterns, was isolated at both excision and reimplantation in four cases (3%). In 10 cases (6%) a different organism was isolated and in 7 cases (5%) reimplantation cultures were positive following negative cultures at the first stage. They could not find any association between positive culture and outcome; however, patients with positive culture at the time of reimplantation received prolonged antibiotics. Overall, 57% of patients with positive reimplantation microbiology received very prolonged (>1 year) antibiotics [14]. Puhto et al. reviewed 107 patients treated with two-stage revision and found 5.2% positive reimplantaion microbiology. Most of the reimplantation cultures were unrelated to organisms cultured at the first stage, which is similar to the results of earlier studies. They treated all patients with positive reimplantation culture as an acute postoperative PJI. The success rate of two-stage revision was not significantly different in patients with positive versus negative microbiology at reimplantation. However, the only case with positive reimplantation culture who failed had the same organisms in both excision and reimplantation [13].

Tan et al. reviewed 267 PJIs (186 knees and 81 hips) treated with two-stage exchange arthroplasty. Here, 33 patients (12.4%) had > = 1 positive culture result at the time of reimplantation. The isolated microorganism at reimplantation was the same as the initial infecting organism in six (18.2%) of the 33 cases. They found that positive intraoperative culture at the time of reimplantation, regardless of the number of positive samples, was independently associated with > 2 times the risk of subsequent treatment failure and earlier reinfection [2]. Akgun et al. reviewed 63 two-stage revision arthroplasties involving 84 THAs and 79 TKAs. They found > = 1 positive culture at the time of reimplantation in 27 patients (16.6%), which was the same initially infection organism in 9 (33%) of them. The risk of the failure of treatment was significantly higher in patients with a positive culture [16].

It seems that the result of culture at the time of reimplantation is related to the outcome of treatment of two-stage exchange arthroplasty. There are several limitations for those studies that implicate reimplantation microbiology do not affect the outcome of two-stage revision for PJI. Firstly, in some studies they found higher rates of failure in patients with positive reimplantation culture, but this finding did not reach statistical significance due to lack of power from the small cohorts available for analysis [13,15]. Secondly, they considered even one positive culture at the time of reimplantation as acute postoperative infection and put the patients on long term antibiotics sometimes longer than a year which makes the success of treatment doubtful [14].

Based on the current evidence, routine cultures during reimplantation should be obtained and relied on. At least four specimens (tissue and fluid) should be taken at second stage surgical reimplantation, using different sterile unused instruments for each sample for subsequent culture. Even single-positive cultures increase the risk of reinfection and failure of treatment and therefore should not be considered as contamination. Patients with positive reimplantation microbiology should receive further antibiotic after reimplantation [2]. Positive culture during reimplantation with the same initial infecting organism or new organisms is independently associated with higher rate of subsequent failure and earlier reinfection [2,16].

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QUESTION 5: Should routine cultures be taken in patients undergoing total joint arthroplasty (TJA) who had a previous open reduction and internal fixation (ORIF) of the same joint (e.g., prior acetabular fracture)?

RECOMMENDATION: Intraoperative cultures should be taken in patients undergoing TJA who have had a prior ORIF of the same joint.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 87%, Disagree: 11%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

TJA in patients with prior ORIF of the affected joint is a common procedure [1]. A subset of these patients undergoes TJA for resulting nonunion, early fixation failure and/or posttraumatic arthritis. TJA after ORIF is commonly referred as conversion arthroplasty and these have been associated with higher complication rates when compared to primary TJA [2–4]. Among those complications, periprosthetic joint infection (PJI) has been identified as one of the causes ranging from 1.6 to as high as 7% [5–7].

The increased risk of PJI in these patients is multifactorial [8]. Studies have identified that any prior surgery to the joint is a risk factor for PJI, both in knees and in hips [9]. Underlying infection has been postulated as one of the reasons ranging in incidence from 11 to 18% [2]. When evaluating TJA candidates with prior ORIF, some authors report that the measurement of preoperative erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) should be performed to identify infections [2]. They conclude that this is an effective method and that efforts should be made to identify and treat underlying infections prior to TJA to reduce the risk of subsequent PJI.

Systemic and local reactions to prior trauma as well as manipulation at the site of arthroplasty may also predispose these patients to infection. Moussa et al. identified positive cultures in 11 hardware cultures out of 21 patients undergoing hardware removal for reasons different from infection, none of these patients had signs of infection [10]. While none of these patients sustained a later infection, none had additional hardware or prosthesis implanted. Positive cultures in clean orthopaedic surgery can range up to 8.3% without correlation with postoperative infection [11]. Again, these patients did not undergo a subsequent TJA. In a different study, Ritter et al. saw that two positive intraoperative cultures at the time of TJA, in patients with prior surgery, develop PJI [12]. They failed to distinguish ORIF only patients and also included in this group failed aseptic TJA.

Performing routine cultures does not come without risk. Cultures are not an inexpensive tool, cost is around $25 U.S. per culture [11]. Depending on how it is collected, there can be different results in the bacterial growth. Chen et al. demonstrated that during the same knee arthroplasty surgery, if the samples are exposed in the operating room, there can be a contamination in the material leading to a false-positive result [13]. Even if there is a positive culture test, it doesn't necessarily indicate an infection.

While intraoperative cultures are not always positive in infected patients, two or more can correlate with a subsequent PJI. Current MusculoSkeletal Infection Society (MSIS) criteria for PJI diagnosis include intraoperative cultures both as major and minor criterion. Therefore, cultures should be included in the workup for possible infection prior to TJA. Literature is consistent in showing that these patients have an increased risk of subsequent PJI given they had a prior surgery on the affected joint.

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QUESTION 6: Is there a role for sonication of implants retrieved during explantation?

RECOMMENDATION: Several studies have demonstrated that sonication of explanted orthopaedic prostheses is a viable method for detecting pathogens, particularly in the setting of culture-negative infections.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 88%, Disagree: 8%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Periprosthetic joint infection (PJI) is an uncommon, but devastating, complication following total joint arthroplasty with serious economic implications [1–3]. Since the management of aseptic implant failure differs from that of PJI, accurate diagnosis is critical [2]. One of the greatest challenges in the treatment of PJI remains the identification of the infective organism. Routine cultures are commonly performed for the microbiological diagnosis of PJI, however, these cultures may be falsely negative, which may complicate management [4]. Prior studies have demonstrated synovial fluid culture sensitivities ranging from 43 to 75% and periprosthetic tissue culture sensitivities ranging from 61 to 73% [5]. Culture sensitivity is dependent upon various variables such as prior use of antibiotics, sampling error, inadequate transport and an insufficient number of viable bacteria retrieved [6].

Investigations have shown that PJI is typically caused by microorganisms forming biofilms on implant surfaces [7,8]. Biofilms are complex bacterial communities capable of self-producing a glycocalyx matrix that protects the cells from environmental and antimicrobial threats [7]. Biofilms can be polymicrobial or possess the ability to recruit other species to allow for permanent attachment to the host tissue and the endoprosthetic surface, thereby increasing antibiotic resistance and metabolic cooperation between all involved bacterial species [8]. Accurate microbiological diagnosis, therefore, depends on the effective disruption of biofilms from implant surface using low-intensity sonication for more sensitive PJI diagnosis than the current conventional methods using a periprosthetic tissue or synovial fluid cultures [9–13]. Sonication before the culture of explanted prostheses has also been shown to enhance bacterial growth in culture by dislodging the sessile organisms [14,15].

Review of available literature shows that sonication fluid cultures (SFC) consistently demonstrates increased sensitivity (78.5% to 97%) in the identification of organism without sacrificing the specificity (81% to 98.8%).[9,10,14,16–19] In a study of 331 patients, Trampuz et al. showed the sensitivity of SFC (78.5%) was significantly superior to tissue culture (60.8%) ($p<0.001$) [10]. They had also shown that use of use of SFC (75%) was more sensitive than tissue culture (45%) when the antimicrobial agent was discontinued within 14 days before surgery [10]. In 2017 Rothenberg et al. used MusculoSkeletal Infection Society (MSIS) criteria and found that SFC was more sensitive than synovial fluid or tissue culture (97 vs. 57%) [17]. Janz et al. have also shown that sensitivity and specificity can be further improved to 100% by separating components into multiple sonication fluid cultures [20].

In contrast to the above results, some studies have shown a lower sensitivity with using SFC suggesting the importance of the technique used [21]. It is also suggested that in early PJI cases sonication is not superior to conventional techniques [22]. As with all microbiological diagnostic tests, the sonication procedure could be potentially contaminated during the process and could result in false-positive results [20,23]. Therefore it is essential to define what constitutes positive SFC. Various studies recommended five Colony Forming Units (CFUs) as a cutoff to limit false-positive results [10,17,24].

While positive histology, periprosthetic tissue and SFC are highly predictive of implant failures in patients with PJI, more than 10% of patients with suspected aseptic loosening are misdiagnosed PJI [25]. Unrecognized or occult infection has been implicated in contributing to "aseptic" loosening of joint prostheses [26]. Studies by Holinka et al. and Janz et al. have shown that all endoprosthetic components are colonized in cases of PJI for revision arthroplasties [14,27]. Investigations to optimize pathogen identification are still ongoing. Studies have indicated that polymerase chain reaction (PCR) of sonication fluid is a promising test for microbiological diagnosis of PJI especially in patients who were on antibiotics [22,28–31]. A limitation of PCR is that identification of bacterial DNA does not necessarily confirm the presence of live bacteria [32]. However, the advantage of PCR is its short processing time (<5 hours) and fully automated procedure [33].

Currently, the microbiological diagnosis of PJI remains a challenge because a gold standard protocol has not yet been established. Cultures are commonly performed for the microbiological diagnosis of PJI, but their sensitivity is influenced by various factors as mentioned earlier. Given the overwhelming literature supporting the increased sensitivity of sonicate fluid to identify pathogens relative to conventional methods, and the feasibility of this technique, we conclude that there is a beneficial role regarding the use of sonication for explanted prostheses in the setting of suspected PJI.

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2.5. DIAGNOSIS: REIMPLANTATION

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QUESTION 1: Are the MusculoSkeletal Infection Society (MSIS) and Interntional Consensus Meeting (ICM) criteria valid for decision-making before reimplantation?

RECOMMENDATION: The validity of the MSIS and ICM criteria for determination of the timing of reimplantation is unclear.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 7%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

George et al. [1] studied 79 patients undergoing reimplantation and found that MSIS criteria had a high specificity (96%) in predicting persistent infection, though the sensitivity was low (26%). They also found that patients who had positive MSIS criteria were at increased risk for reinfection after reimplantation. Kheir et al. [2] also investigated the MSIS criteria in patients who were undergoing two-stage exchange for periprosthetic joint infection (PJI) and reported a sensitivity of 25% and a specificity of 87% for detecting persistent infection. The authors further investigated the utility of the leucocyte esterase (LE) strip test and found that the LE strip test was positive in 22.2% of culture-positive and 4.4% of culture-negative cases. The LE test was negative in all patients who had not failed at their latest follow-

up, showing a great negative predictive value. In another study of 32 patients undergoing reimplantation, the authors found that the MSIS criteria had a very low sensitivity (0%), though the specificity was high (89%) [18]. Therefore, the MSIS criteria have a limited utility in the setting of reimplantation; nevertheless, it appears to be useful for ruling in infection.

Cultures are an integral part of the MSIS criteria. Multiple studies examining the role of reimplantation microbiology have found that positive cultures were associated with an increased risk for failure [3–10]. Tan et al. [8] reported that the risk of failure due to infection was higher (odds ratio (OR) = 2.5) in those with a positive culture during reimplantation. The study did not show a difference in the reinfection rates between a single and multiple (≥ 2) positive cultures. Although cultures are useful in predicting failure, the results of intraoperative cultures are not available before reimplantation. Prolonged antibiotics are recommended in patients who have positive intraoperative cultures. In a study by Murillo et al. [6], the authors had seven patients with positive intraoperative cultures during reimplantation and treated them all with 6-8 weeks of parenteral antibiotics. Patients were followed for a median of 30 months and none of them had recurrence of infection. The authors concluded that preoperative cultures can help identity patients who can benefit from an additional debridement procedure with spacer exchange. Mont et al. reported that the reinfection rates were lower in patients who underwent an additional debridement procedure if the preoperative cultures were positive prior to reimplantation [11].

Intraoperative frozen sections can help formulate a decision in a timely manner compared to intraoperative cultures. Studies examining the utility of frozen sections have consistently shown that frozen sections had a high specificity and low sensitivity in detecting persistent infection [1,12,13]. Therefore, a positive result should be treated as infection and reimplantation should be delayed, while a negative result may not be able to exclude infection.

Erthrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been widely used to monitor response to treatment. Currently, there is limited evidence to support a specific cut-off for ESR and CRP. Although some studies have reported that both ESR and CRP decrease between the stages of a two-stage exchange protocol in patients with resolution of infection, their corresponding values are often above the MSIS cut-offs even in patients whose infection has clinically being cleared [14–16].

Synovial markers such as white blood cell (WBC) count and polymorphonuclear leukocytes (PMN) % have shown promising results in determination of reimplantation timing, however the optimal cut-off threshold for WBC count might be lower than the MSIS threshold of 3,000 cells/μL [14,15,17].

One of the major concerns with the studies evaluating the MSIS criteria or its components is the lack of a gold standard for diagnosing PJI or determining persistent infection. Most studies have compared the MSIS criteria with failure after reimplantation or the clinical decision to perform a spacer exchange [1,2,18]. However, it is unclear whether failure after reimplantation is an accurate representation of an undetected persistent infection or a newly acquired PJI. In a multicenter study of 92 patients who developed failure after reimplantation, only 32% of the patients had an identical organism at failure suggesting that many patients may be having a new infection rather than a persistent infection [9]. Another limitation of most studies is the presence of missing data [1,2,18]. As diagnostic tests are often performed in patients with an uncertainty in the diagnosis, it is possible that many patients with obvious infection may not have had all the appropriate tests performed. This can underestimate the utility of the MSIS criteria and maybe partly responsible for the low sensitivity of the MSIS criteria.

In summary, very few studies have evaluated the role of MSIS criteria in determining the reimplantation timing. Therefore, it is unclear whether the MSIS or the ICM criteria are a reliable tool for this matter. Cultures constitute a major part of MSIS criteria and a positive culture at reimplantation has been shown to increase the risk of failure in numerous studies. Frozen sections are reported to have a high specificity, though their sensitivity is limited. Synovial markers such as WBC counts, PMN % and the LE test had better results in diagnosing persistent PJIs compared to serum markers. Although ESR and CRP decrease between the stages of a two-stage exchange treatment, they cannot be reliably used to detect persistent infection at the current thresholds. There is a dire need for an accurate diagnostic test to determine optimal timing of reimplantation in patients undergoing surgical treatment for PJI.

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QUESTION 2: What metrics should be considered to determine the timing of reimplantation after two-stage exchange arthroplasty of the infected hip or knee?

RECOMMENDATION: There are no definitive metrics to allow determination of optimal timing of reimplantation. Thus, timing of reimplantation should consider resolution of clinical signs of infection, down-trend in the serological markers and results of synovial analysis, if aspiration is performed.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 96%, Disagree: 3%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Because optimal timing for reimplantation is unknown, most surgeons prefer to rely on a combination of clinical evaluations, such as clinical evidence of infection control and normalized laboratory values after a period of antibiotic therapy [1]. There is no gold standard that can guide surgeons to determine the optimal time of reimplantation [2]. Various serum and synovial markers have been studied to identify the most accurate test for screening for persistent periprosthetic joint infection (PJI). A common finding of most of the studies is a high specificity, but low sensitivity.

Serum Analysis

Several serum markers have been evaluated for PJI, but only a few prior to reimplantation. Serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been widely evaluated for diagnosis, monitoring treatment and evaluating their role in identifying the optimal timing of reimplantation [2–9]. Although a decreasing trend in both markers is seen during the interval period, they can still be elevated in patients that are considered to have a treated infection and have also been seen to be normal in persistent infection. In different studies, no cut-off values could be determined and there were no significant differences in average ESR and/or CRP values at time of reimplantation between infected and non-infected cases [3,7].

Interleukin-6 (IL-6) has been recently studied among other biomarkers in PJI. It has been seen that it may have a role in defining persistent infection prior to reimplantation, although stronger evidence is needed [10]. A recent study by Shahi et al. [11], showed promising results in determining the reimplantation time using serum D-dimer test. In their cohort, 29 patients underwent reimplantation surgery for PJI. Five patients had elevated D-dimer levels at the time of reimplantation, two of which had a positive culture from intraoperative specimens (*Staphylococcus epidermidis* in one patient and *Cutibacterium acnes* (*C. acnes*) in the other patient). Both of those patients subsequently experienced failure due to infection. Based on the results of this study, D-dimer outperforms both ESR and CRP for determining the timing of reimplantation. The corresponding CRP and ESR values were falsely negative in both of these patients (a CRP level of 8 mg/L and an ESR of 20 mm/hr in one patient; a CRP level of 1 mg/L and an ESR of 9 mm/hr in the other patient). Ongoing clinical research is currently investigating the utility of D-dimer in determining the timing of reimplantation surgery. D-dimer is an inexpensive and widely available test that can aid in identifying the timing of reimplantation.

Joint Aspiration

Synovial fluid aspiration and analysis for cell count, microbiological culture and biomarkers prior to reimplantation is also widely being used to detect persistent infection. Studies on synovial fluid WBC and differential analysis are contradictory [6–9,12,13]. Kusuma et al. [7], showed that prior to reimplantation, synovial fluid white blood cell (WBC) and differential analysis are poor markers of persistent PJI in the knee. Conversely, Shukla et al. (6) found pre-reimplantation synovial WBC count to be highly diagnostic of persistent infection in the hip. Zmitowski et al. [12], reported elevated synovial WBC count and polymorphonuclear lukocyctes (PMN)% statistically significant in patients with persistent PJI but did not provided useful threshold to identify patients with persistent PJI. Almost all studies evaluating microbiological culture of joint aspirate report a very low sensitivity, which means persistent infections are not detected [8,9,13,14]. In addition, Mühlhofer et al, [8] identified that microbiological synovial fluid analysis can also be misleading due to false positive cultures.

Kheir et al, [15] reported on the use of the leukocyte esterase (LE) as a screening test for persistent infection. This test demonstrated a high specificity (100%), but low sensitivity (25%). A positive LE result had a high predictive value of failure of reimplantation. Frangiamore et al, [16] evaluated synovial fluid cytokines to determine the highest diagnostic accuracy for PJI. IL-6 and IL-1β showed the greatest decrease between first and second stages; these could potentially be used to monitor PJI treatment response. Due to the low sensitivity of these tests, they fail to provide a definite answer as to the infection status.

MusculoSkeletal Infection Society (MSIS) Criteria

The efficacy of MSIS criteria for determining infection resolution in PJI has also been evaluated [15–17]. Despite the clinical importance of these criteria, the lack of sensitivity of these tests do not make them useful in diagnosing persistent infection. Frangiamore et al. reported a specificity of 89% and sensitivity of 0% for MSIS criteria to rule out PJI after the first-stage [16]. Another study by Georges et al. [17], evaluated 97 patients undergoing reimplantation and also demonstrated a high specificity but low sensitivity for MSIS criteria

for diagnosing persistent infection. They concluded that MSIS criteria should be evaluated at the second stage of revision arthroplasty because they discovered that performing reimplantation in a joint that is MSIS-positive for infection significantly increased the risk for subsequent failure.

Intraoperative Tests

Intraoperative frozen sections have also been used as a reliable indicator of infection during revision arthroplasty. These have been well studied for infection eradication in revision surgeries. Although there is still debate about the optimal diagnostic cut-off (number of PMNs per high-power field), authors have recommended that reimplantation should be delayed when frozen sections are positive. However, intraoperative frozen sections are not reliable enough for ruling out persistent infection because of a low sensitivity [17–21]. Della Valle et al. showed a sensitivity of 25% in their study (18). More recently, George et al. reached a 50% sensitivity, despite the fact that these specimens were evaluated by a highly specialized pathologist [17]. Intraoperative microbiology stains are not recommended due to their very low sensitivity [22–24].

We consider that a combination of available diagnostic variables should be evaluated to determine the infection status of a patient prior to reimplantation. A surgeon must rely on this strategy and clinical judgment to proceed with reimplantation.

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QUESTION 3: Is normalization of serological markers necessary prior to reimplantation arthroplasty performed as part of a two-stage exchange?

RECOMMENDATION: No. A trend and decline in C-reactive protein (CRP) and erthyrocyte sedimentation rate (ESR) is expected, but we still recognize that there are certain cases in which reimplantation may be performed despite abnormal levels of ESR and CRP. Surgeons should not wait for complete normalization of the inflammatory markers as this may not occur in some patients and/or take a long period of time.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 4%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Among the efforts to improve the effectiveness of the two-stage exchange for periprosthetic joint infection (PJI) are the attempts to identify persistent infection, by the use of primary and secondary inflammatory markers, before reimplantation.

A decline in ESR and CRP levels in conjunction with the absence of clinical signs of infection are often believed to be an indication that it is safe to proceed with reimplantation. Ghanem et al. [1] demonstrated that in patients with recurrent infection, ESR and CRP mean levels, before the second stage, were similar to those in patients whose infection had been successfully treated. Similarly, Kusuma et al. [2] found no significant difference in test results between the persistently infected and non-infected groups before second-stage surgery. In both studies, the authors constructed a retrospective review with the intent of determining a specific value of ESR, CRP, or both that could be used to detect continued infection prior to reimplantation. They found that no such value could be determined and that the ESR and CRP of those with and without infection were similar.

The persistently elevated ESR and CRP levels, at the time of reimplantation, were found in 54% and 21% of the patients, respectively. Also, Shukla et al. [3] reported that the mean ESR and CRP levels significantly decreased between stages, but remained elevated in 62.5 and 27.5% of the patients in whom the infection had been eradicated.

Kubista et al. [4] found no statistically significant differences in mean values for CRP or ESR before resection or reimplantation when comparing the treatment failure group to the control group.

One study did note that there was a weak trend between the level of inflammatory markers prior to reimplantation and the subsequent outcome in total knee arthroplasty (TKA) patients undergoing two-stage exchange arthroplasty [5]. In a similar study for total hip arthroplasty (THA), no association between successful second stage reimplantation and pre-reimplantation levels of ESR and CRP could be detected [6]. Likewise, the values did not differ between failure and success groups in a series reported by Mortazavi et al. [7]. Therefore, the available evidence suggests that serologic markers cannot be the only factor in guiding the surgeon for the appropriate timing of reimplantation.

While some authors advocate for waiting until normalization of inflammatory markers ESR and CRP [8–11], many others [12–16] rely upon a downward trend of the markers before proceeding with reimplantation. In those cases, in which no constant decrease of the values is observed, some prefer to promote spacer exchange instead of reimplantation [17,18].

The level of inflammatory markers may remain elevated in patients with inflammatory conditions which can cloud the picture [19,20]. The inflammatory markers should still be measured in patients with inflammatory conditions both for the purpose of diagnosis of PJI and also determining the timing of reimplantation. George et al. [21] analyzed the diagnostic utility of ESR and CRP to detect, at the time of the second stage, persistent infection in patients with inflammatory arthritis. At the time of reimplantation, ESR and CRP remained elevated above the MusculoSkeletal Infection Society (MSIS) threshold in many patients with inflammatory arthritis. The authors, however, did conclude that persistently elevated serological markers should not always be presumed to be the result of underlying inflammatory arthritis, and could suggest an ongoing infection [21].

Previous studies have examined the role of other serum markers for infection. One such marker is Interleukin-6 (IL-6) that has been shown to be highly predictive of PJI in patients undergoing revision surgery in one study [22]. A cut-off serum value of 8 pg/ml is a sign of an absence of infection and perhaps an indication for reimplantation. Other studies have not been able to prove value for serum cytokines but have suggested that if such markers are measured a downtrend between the two stages may provide an important guide for clinicians to monitor the treatment response [23]. Recently the serum D-dimer was reported to have a great potential for diagnosis of PJI [24]. The utility of this test for optimal timing of reimplantation is being evaluated and the preliminary results presented in the American Academy of Orthopaedic Surgeons (AAOS) annual meeting, by the same authors, appeared to be encouraging.

Regarding the analysis of synovial fluid, Zmistowski et al. [25] postulated that synovial fluid analysis, even though of unclear utility, may detect persistent PJI before reimplantation. Shukla et al. [3] observed that white blood cell (WBC) count could identify persistent infection with a cut-off value of 3,000 cells/μL. To the contrary, Muhlhofer et al. [26] could not establish cutoff values for CRP, leucocytes, WBC count and polymorphonuclear (PMN) percentage, thereby observing that no reliable markers were indicative of persistence of infection. CRP and leucocytes were often found to be elevated, even when the infection had been controlled.

A synovial biomarker with great promise is leucocyte esterase (LE). A study by Kheir et al. found that a positive LE test (defined as ++) at the time of reimplantation was indicative of persistent infection and predicted a later failure with great accuracy [27]. Another recent study from the same institution by Tarabichi et al. [28] posited that analysis of LE, when used in conjunction with serologic screening, is a powerful point of-care test for diagnosis of PJI and timing of reimplantation. Based on the available evidence it is worthwhile to consider the use of LE strips at the time of reimplantation that can provide the surgeons with additional and definitive analytical information.

Based on the current evidence, serum inflammatory markers, ESR and CRP, are not believed to be reliable on their own in determining the presence of infection. It is our understanding and recommendation that these markers should still be monitored between the two stages and a decline in their value sought before proceeding with reimplantation. The value of the serum ESR and CRP in timing the reimplantation may be improved if the result of synovial fluid analysis, in particular using the LE strip test, and possibly other serum markers, such as D-dimer, are combined. There is a need for future studies to identify the most appropriate marker that may be indicative of persistent infection.

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QUESTION 4: What is the importance of two-week antibiotic holiday prior to reimplantation?

RECOMMENDATION: Unknown. There is no conclusive evidence to support the need or the ideal length of an antibiotic holiday prior to reimplantation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 7%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Two-stage exchange arthroplasty continues to be the preferred method of treatment for chronic periprosthetic joint infections (PJIs) in the United States and Europe. Traditionally, the procedure involves removal of all foreign material and a six-week period of ensuing antibiotic treatment. Prior to reimplantation it is customary to implement a 14-day antibiotic-free interval, known as a drug holiday, intended to allow for "emergence" of residual infection [1]. During this period serological testing and synovial aspiration are usually performed to ensure that infection is under control prior to proceeding with reimplantation. However, this widely implemented therapeutic option has remained controversial [2] because of the paucity of the systemic antibiotic treatment after six weeks, which can lead to the persistence of an infection and the development of multiple drug-resistant bacterial strains.

In addition, the accuracy of serological tests and synovial aspiration under ongoing systemic antibiotic therapy is debatable. Ghanem et al. [3] and Spangehl et al. [4] have reported that data regarding the value of serological markers and synovial aspiration between the stages have been published using heterogeneous cohorts, short follow-up periods and inconsistent antibiotic-free intervals. Meanwhile, some studies have suggested the abandonment of the systemic antibiotic pause after six weeks in favor of a continuous antibiotic administration [5,6].

Bejon [7] et al. (2010) retrospectively reported on 152 patients with periprosthetic joint infection (PJI) who were treated with two-stage revision with a success rate of 83% over a median follow-up duration of 5.7 years; this is within the reported range of success rates [7]. The reimplantation was preceded by a two-week antibiotic-free period in 88% of the cases. However, the microbiology was positive in 3 of 18 patients (16%) without a two-week antibiotic-free period compared with 18 of the 134 patients (13%) with a two-week antibiotic-free period. At reimplantation, more knee joints were culture positive than hip joints, despite being less frequently culture positive at the first-stage excision. Spacers were used in all knee joint revisions; however, they were rarely used for the hips (13%). They did not use aspiration but waited during the two-week antibiotic-free period and decided whether to perform reimplantation based on the clinical appearance. Most unexpected debridements following the first

stage were performed without discontinuing the antibiotics. They concluded that there was no evidence supporting the application of an antibiotic-free period prior to reimplantation and routine reimplantation microbiology. The authors did not find evidence to support the implementation of an antibiotic holiday.

Müllhofer [5] et al. (2018) examined 112 patients who were MusculoSkeletal Infection Society (MSIS) criteria-positive for prosthetic joint infection, including 45 patients with total hip arthroplasties (THAs) and 67 with total knee arthroplasties (TKAs). They treated all patients with a two-stage protocol using a mobile polymethal methacrylate (PMMA) spacer after a 14-day antibiotic-free interval, during which serological markers (C-reactive protein (CRP) and leucocytes) were assessed and synovial aspiration (white blood cell (WBC) count, polymorphonuclear cell (PMN) percentage and microbiological culture) was performed, and the outcomes were compared with those of their long-term follow-up (mean follow-up, 27 months; range, 24 to 36 months). They identified no reliable marker that was suggestive of the long-term persistence of an infection. CRP and leukocytes were often elevated although the infection was controlled. Normalized serum markers did not exclude the persistence of an infection during the follow-up period.

The synovial analysis of WBC count and PMN percentage did not support their well-investigated diagnostic reliability before stage one. The authors pointed out that microbiological synovial fluid analysis was often misleading because of false-positive microbiological cultures, which resulted in overtreatment. In addition, they emphasized the need for high-quality antibiotic treatment, including biofilm-active antibiotics, without any antibiotic holiday for diagnostic reasons. Moreover, they suggested that the reliability of serum markers increases if the time between the first and second stages is prolonged up to 6 months or one year, accounting for a poor functional outcome and increased psychosocial burden [3,5].

In contrast, Janz [8] et al. (2016) have reported remarkably high sensitivity (95%) with low specificity (20%) for serum CRP for predicting the persistence of the infection of resection arthroplasty hips without PMMA spacers. In their study group, the interval between the removal of an implant and the performance of the second stage was up to several months in the Girdlestone-hip group, whereas the cohorts of Müllhofer [5], Kusuma et al. [9] and Ghanem et al. [3] exhibited a standardized timeline with a diagnostic workup eight weeks after explanation.

Boelch [6] et al. (2018) retrospectively analyzed 92 aspirations before the planned joint reconstruction during the two-stage exchange with hip spacers. The PJI was diagnosed according to the Clinical Practice Guidelines by the Infectious Diseases Society of America.

The mean duration from the index surgery to the prosthesis removal was 58.75 months (median, 14.38 months). In the study, 47.8% of the prosthesis removal were primary revisions, and 57.6% patients were males. In addition, the mean age at the prosthesis removal was 67.46 years, and the mean Body Mass Index (BMI) was 29.8 kg/cm^2. An articulating (91.3%) or a resection arthroplasty spacer (8.7%) was implanted at the surgeon's preference. Spacers were molded by hand with a Steinman pin as an endoskeleton. In addition, Palacos R+G and 2 gm of vancomycin per 40 cm^3 of the batch were routinely applied. If preoperative cultures from aspiration exhibited no growth, then antibiotic therapy was initiated in combination with an aminoglycoside and a cephalosporin.

In case of bacterial detection, antibiotic therapy was modified according to a microbiologist's recommendation. In this study, the mean duration of intravenous antibiotic administration was 18.5 days, followed by a course of oral antibiotic therapy for a mean of 17.0 days.

The mean combined duration of antibiotic therapy was 34.4 days, and the mean drug holiday was 15.3 days. Precisely, 72.8% of inter-stage aspirations were performed after a drug holiday of at least 14 days. Aspiration was performed under sterile conditions. Their results implicated that neither the synovial fluid culture nor the synovial leucocyte count at the inter-stage aspiration during the two-stage exchange of the hip with a spacer was consistent as a standard approach for ruling out the persistence of the infection.

Thus, the authors preferred reconstruction or spacer exchange without any cessation of systemic antibiotic therapy, and they strongly discouraged aspiration during the two-stage exchange and instead recommended considering a high CRP before prosthesis removal and reconstruction suggestive of an increased risk of the persistence of an infection. Our literature review highlights that no single factor could be used alone when evaluating the success of two-stage arthroplasty in eliminating infection.

Thus, we must rely on a combination of clinical evaluation, imaging, serologic tests and biopsies to ascertain the timing of reimplantation. Additionally, there seems to be little evidence for deferring reimplantation until all serologic markers are normalized, which, perhaps, can lead to prolonged disability and ultimately cause soft tissue contractures and further bone loss [3].

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QUESTION 5: What is the diagnostic accuracy of joint aspiration of a cement spacer in conjunction with clinical evaluation, imaging, serologic tests, and biopsies? Should it routinely be performed prior to reimplantation?

RECOMMENDATION: The diagnostic accuracy of joint aspiration prior to reimplantation is not known. None of the parameters being used to diagnose periprosthetic joint infection (PJI), and their respective thresholds, have been determined for aspiration. The decision to perform aspiration should be made based on the index of suspicion for persistent infection and individualized.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 4%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Until today none of the diagnostic methods for PJI have demonstrated 100% specificity or sensitivity [1]. Therefore, a diagnostic method that involves a combination of clinical evaluation, imaging, serologic tests, as well as aspirate tests and biopsies, needs to be established for confirming the diagnosis of PJI. Two-stage exchange arthroplasty is comparable with one-stage exchange arthroplasty in that all the components are removed at the time of surgery. In contrast to one-stage arthroplasty, in two-stage surgery cases, a temporary antibiotic delivery device (a spacer) is implanted locally, and systemic antibiotics are administered intravenously for four to six weeks, with an antibiotic holiday of two to eight weeks prior to reimplantation for confirming the elimination of the infection [2–4] and to ensure that the samples collected at reimplantation for microbial culture do not give negative results owing to previous antibiotic use [4].

The two-stage reimplantation procedure for managing infected total knee arthroplasty (TKA) was first described by Insall et al. [5] in 1983. According to them, the first stage includes the removal of all the foreign materials from the joint. Thereafter, the debridement of all soft tissues, bone, synovectomy, irrigation and reaming of the medullary canals is performed. After joint preparation, antibiotic-loaded cement beads and/or a static or articulating spacer is inserted, followed by the closure of the soft tissues and the skin. The patient is then prescribed antibiotics for an extended period of time. Intravenous antibiotics are most commonly used and are selected on the basis of the sensitivities of the infecting organisms, as determined from the preoperative and intraoperative microbiologic cultures [5].

In 2000, Mont et al. [6] conducted a prospective study involving 34 patients who had undergone an aspiration before reimplantation, four weeks after antibiotic administration was discontinued. The authors concluded that cultures of knee aspirates had 75% sensitivity, 100% specificity, 100% positive predictive value, and 97% negative predictive value.

Beckerom and Stucky [7] (2006) studied the cultures of aspiration fluid from 68 infected knees in 67 patients; they reported 32 true positives, 17 true negatives, 6 false positives, and 13 false negatives and concluded that preoperative aspiration had a positive predictive value of 71% and a negative predictive value of 74%. They stated that a positive aspiration result may indicate prosthesis infection; however, a negative result does not rule out infection, and one must consider a coagulase-negative Staphylococcus infection in such cases.

Meermans and Haddad [8] (2010) prospectively followed 120 patients with assumed infection of total joint arthroplasty, including 64 with total hip arthroplasties (THAs) and 56 with TKAs. All patients had undergone aspiration with culture and biopsy. They inferred that the sensitivity was 83% for aspiration, 79% for biopsy, and 90% for the combination of both the techniques. The specificity was 100% for aspiration, biopsy and the combination. Their overall accuracies were 84%, 81%, and 90%, respectively. They concluded that routine aspiration should be followed by a biopsy in the workup of septic joints.

Lonner et al. [9] (2001) published a study of 34 infected knee prostheses, where aspiration was performed for the detection of persistent infection prior to reimplantation and after the completion of a four to eight week course of antibiotics. They concluded that knee aspiration following resection arthroplasty had sensitivity and positive predictive value of zero, a negative predictive value of 75%, and a specificity of 92%. They further stated that a negative result of joint aspiration after resection arthroplasty may not necessarily rule out current infection. The average antibiotic-free interval in all patients was 20 days; patients with false-negative results of aspiration had an average antibiotic-free interval of 11.5 days compared with 26 days among all other patients.

In addition, the study performed by Ghanem et al. [10] (2009) reported that a negative result of aspiration of the knee did not rule out infection. They observed false-negative aspiration in 15% of their cases, similar to the report by Lonner [9] et al.

Sanchez-Sotelo et al. [11] (2009) focused on long-term reinfection-free survival and mechanical durability; they retrospectively reviewed 168 patients (169 hips) with infected arthroplasty, all of whom had undergone two-stage reimplantation for an infected THA from 1988 to 1998. In the second stage, the femoral component was fixed with antibiotic-loaded bone cement in 121 hips, while the other femoral components and all the acetabular components were uncemented.

The minimum follow-up time was 2 years (mean, 7 years; range, 2–16 years). At the most recent follow-up, 12 hips (7.1%) had undergone re-operation for reinfection, and 13 hips (7.7%) were revised for aseptic loosening or osteolysis. Aseptic loosening occurred on one or both sides of the joint in 24 hips (14.2%). The 10-year rates for survival without reinfection and mechanical failure were 87.5% and 75.2%, respectively. Nineteen hips dislocated and eight underwent revision surgery for instability. The two-staged procedures included the removal of all the prosthetic components, cement (if present), and all the foreign bodies followed by intravenous antibiotic therapy and delayed reimplantation of THA. They applied a spacer made of antibiotic-loaded polymethyl methacrylate in 31 hips, while the remaining hips underwent resection arthroplasty for the time interval between implant removal and reimplantation.

In the 23 hips with negative intraoperative cultures, infection was diagnosed on the basis of positive intraoperative pathology (13 hips), frank purulence (nine hips, six with positive pathology), positive preoperative aspiration (14 hips, seven with positive pathology)

and/or macroscopic evidence of infection. The average duration of intravenous antibiotic therapy was 6 weeks (range, 3–18 weeks). The median duration of the interval between the resection and reimplantation was 9.4 months (range, 3–18 months). After reimplantation, antibiotics were discontinued when the intraoperative cultures were finalized, except in 16 patients (16 hips) with chronic oral suppression antibiotic therapy.

Kusuma et al. [12] (2011) have determined serology (erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP)) and aspiration (synovial white blood cell (WBC) count) to be predictive parameters for determining the appropriate timing for definitive second-stage reimplantation. These were compared when stopping antibiotic treatment prior to the second-stage procedure. The WBC count in the synovial fluid was found to be the most reliable indicator of infection resolution. However, the researchers were unable to launch any definitive outlines indicative of persistent infection.

Newman et al. [13] retrospectively evaluated 77 hips undergoing aspiration before a second stage reimplantation and found a sensitivity of 30% and specificity of 100% in detecting infection. Similarly, Preininger et al. [14] found that pre-reimplantation aspiration cultures had a high specificity (100%), but low sensitivity (21%).

Although a majority of the studies report a high specificity with respect to cultures, the utility of other aspiration tests is less clear. Shukla et al. [15] found that WBC counts had an area under the curve (AUC) of 0.91 at cut-off of 3,528 cells/μL (sensitivity, 78%; specificity, 96%), whereas polymorphonuclear (PMN) % had an AUC of 0.81 at cut-off of 79% (sensitivity, 78%; specificity, 82%). Newman et al. [13] reported a sensitivity and specificity of 47% and 87% for WBC counts (AUC = 0.67), and 76% and 80% for PMN % (AUC = 0.78), respectively at the MusculoSkeletal Infection Society (MSIS) thresholds of 3,000 cells/μL and 80 PMN %. They also found that when any of the aspiration results were positive for infection (WBC >3,000 cells/μL or PMN % >80 or positive culture), aspiration had a good diagnostic performance (AUC = 0.82). Additionally, they found that lowering the threshold for WBC count significantly improved the diagnostic sensitivity (47 - 76%) while slightly decreasing the specificity (87 - 78%). On the contrary, Hoell et al. [16,17] reported poor diagnostic performances for WBC counts in their two studies (AUCs of 0.37 and 0.56), though the cut-off obtained was close to 1,000 cells/μL. Kheir et al. [18] found that leukocyte esterase (LE) test performed on synovial fluid had a sensitivity and specificity of 26% and 100%, respectively (AUC = 0.56) for detecting persistent infection. They also found that a positive LE test was associated with increased risk of reinfection after the reimplantation surgery.

Most of the studies were performed in a retrospective manner causing an inherent bias in patient selection and were of moderate or low quality [19]. A major concern while interpreting the studies assessing the utility of aspiration is the uncertainty regarding the gold standard test to diagnose persistent infection. Many studies compare the aspiration results to intraoperative cultures, histology or other markers at time of reimplantation, while some studies compare to subsequent failure after reimplantation. Lack of adequate fluid (dry taps) is another concern while performing preoperative aspirations on spacers [13]. Sometimes, saline lavages are performed in an attempt to obtain fluid when such dry taps are encountered. Newman et al. [13] compared the accuracy of aspiration performed with and without a saline lavage, and found that synovial WBC counts and PMN % were noticeably affected by lavage, while culture results were less susceptible to lavage.

In summary, it appears that cultures obtained before the planned second stage are helpful in ruling in persistent infection. A patient with positive culture is likely to benefit from an additional debridement. However, a negative culture does not rule out persistent infection and additional clinical, and laboratory markers should be considered in these patients. WBC counts and PMN % have demonstrated good diagnostic utility, though the WBC cut-off might be lower than the MSIS threshold.

It is well known, that the most important factors in favor of routine aspiration are its reliability, low cost and simplicity of application in an outpatient clinic. Given the studies [8,12] as Level II, diagnostic studies emphasizing the diagnostic accuracy of an aspiration of a cement spacer following a drug-holiday in literature, we conclude that aspiration of a cement spacer in conjunction with clinical evaluation, imaging, serologic tests and biopsies has high diagnostic accuracy and may be performed before reimplantation based on the index of suspicion for persistent infections [20,21].

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QUESTION 6: What intraoperative metrics can be utilized at the time of intended reimplantation to help decision-making and reduce the risk of subsequent recurrence?

RECOMMENDATION: Intraoperatively, frozen section and leukocyte esterase (LE) strip test can be used as decision-making metrics for reimplantation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 66%, Disagree: 25%, Abstain: 9% (Super Majority, Weak Consensus)

RATIONALE

The intraoperative decision-making process for reimplantation must be based on metrics that are fast (due to time constraints), accurate to reduce the risk of recurrence and reliable so that such metrics can be reproduced in many scenarios.

Frozen Section (FS)

Intraoperative FSs have been used as a fast and accurate indicator of infection during reimplantation due to high specificity. Most of the studies recommend withholding reimplantation in the presence of positive results. Nonetheless there is a debate regarding optimal cutoff for the number of polymorphonuclear cells (PMNs) per high-power field and whether this should be a quantitative or qualitative analysis. The primary reason FS is not universally accepted as a decision-making marker is its reliability. FS continues to have a low sensitivity (between 25 - 50%) in the presence of infection [1–5]. FS is also dependent on a highly specialized pathologist with experience, which is evident in a study published by George et al. where even in the presence of a highly trained pathologist, the sensitivity only reached 50% [5]. Gram and fungal stains have very low sensitivity [6–8], and therefore are not recommended.

Leukocyte Esterase (LE)

The LE strip test has the advantages of being a fast, accurate and reliable test. This is supported by several recently published studies and a meta-analysis [9–22]. These publications show that LE has a sensitivity that ranges from 49% up to 95%, and a specificity that ranges from 82 - 100%. Some papers also have shown a positive predictive value (PPV) from 71.5 to 100%.

One of the limitations observed with LE, being a colorimetric assay, was the potential for inaccurate readings in the presence of a bloody sample. A recent study by Li X et al. [23] showed that when a bloody sample is centrifuged, the LE continues to have excellent sensitivity and specificity (92 and 93.1% respectively), making it still a very reliable test for intraoperative decision-making. Another concern when LE started to be widely used was its accuracy in the presence of adverse local tissue reactions (ALTR), namely metallosis. Tischler et al. [12] demonstrated that LE combined with PMN % was reliable in ruling out infection in 92.9% of the cases evaluated.

Alpha-Defensin

The alpha-defensin test as a reliable synovial biomarker for the diagnosis of infection was introduced by Deirmengian et al. [14] Since then, newer techniques have been developed which achieve similar results in a faster fashion. Alpha-defensin lateral-flow immunoassays [24–31]are faster and have a sensitivity that ranges from 64.7 - 94.5%, a specificity with a range of 87 - 99.6%, a positive predictive value (PPV) from 74.6 - 98.1%, and a negative predictive value (NPV) from 83.7 - 98.2%. However, a few studies [29,30] have demonstrated that the immunoassay test performed in the laboratory setting is more accurate than the lateral-flow technique, and provides sensitivity ranges from 83.6 - 97.1%, specificity ranges of 97 - 100%, PPV ranges from 94.9 - 100%, and NPV ranges from 89.9 - 98.2%.

As with LE, other factors can impact the accuracy of Alpha-defensin testing. The specificity and PPV can decrease in the presence of ALTR [24] and crystal deposition arthroplasties [31].

Interleukins

Another lateral-flow immunoassay technique being used for the diagnosis of PJI involves interleukins, specifically Interleukin-6 (IL-6). This intraoperative test allows for a rapid assessment of the cytokines within the synovial fluid. This technique is already in use with an acceptable specificity but relatively low sensitivity. However, when IL-6 is measured in the lab with radioimmunoassay techniques, it is more accurate [32].

Despite having these time-tested and novel techniques, the surgeon continues to rely on a combination of preoperative testing, intraoperative clinical judgment and the interpretation of these intraoperative metrics to decide whether it is safe to proceed with reimplantation and avoid the risk of PJI recurrence.

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QUESTION 7: What is the diagnostic accuracy of a frozen section (FS) during reimplantation surgery? What thresholds should be used in this context?

RECOMMENDATION: Adequate peer-reviewed literature exists to support either of two diagnostic thresholds for supporting the diagnosis of periprosthetic infections of the hip and knee: 5 neutrophils (PMNs) in each of at least 5 high power (400X) microscopic fields (HPF), or 10 PMNs in each of at least 5 HPFs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 83%, Disagree: 10%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

A common method of treating periprosthetic infection of the hip or knee is two-stage exchange [1], but it can be difficult to determine if and when the infection has been adequately treated and the infected joint is ready to receive a new implant. The tests commonly used to help diagnose infection at revision arthroplasty, such as serologic tests, microbiologic culture, and the cell count with differential of aspirated joint fluid may have been influenced by the previous surgery as well as an antibiotic-containing spacer and may not have the same predictive value as when they are applied at revision arthroplasty [2].

One of the few tests that can be performed during a reimplantation or revision arthroplasty operation is the interpretation of a FS of

TABLE 1. Study results showing similar values as reported for frozen sections obtained at primary arthroplasty

Reference	Cases	Sensitivity	Specificity	PPV	NPV	Accuracy
[10]*	64	25%	98%	50%	95%	94%
[11]**	79	50%	94%	50%	94%	90%
[13] (FS)**	47	56%	95%	73%	97%	87%
[13] (PS)**	47	89%	94%	80%	97%	94%

PPV, Positive Predictive Value; NPV, Negative Predictive Value; FS, Frozen Sections; PS, Permanent Sections

* Threshold: 10 PMN in each of at least 5 HPF

** Threshold: 5 PMN in each of at least 3 HPF

periprosthetic tissue. In that context, the presence of acute inflammation, as characterized by neutrophils (neutrophilic granulocytes, polymorphonuclear leukocytes, (PMNs), suggests ongoing infection [3-6]. The tissue block from which that section was prepared is then formalin fixed and processed, along with additional tissue samples as a "permanent section" to be interpreted a day or two later. As a rule, the higher the tissue concentration of neutrophils, the more likely the joint is infected, but there is controversy about the best threshold to help diagnose or rule out infection. Several systematic reviews have identified adequate high-quality studies support thresholds of either 5 or more neutrophils in each of 5 HPFs or 10 or more neutrophils in each of 5 HPFs to support the diagnosis of infection [3,7] at the time of revision arthroplasty. Several other thresholds have also been suggested [8,9] and the results of FS have also shown good correlation with the modified MusculoSkeletal Infection Society (MSIS) criteria for periprosthetic infection [4]. However, few studies have addressed the accuracy of FSs to diagnose persistent infection at the second stage reimplantation of a two-stage revision arthroplasty for known periprosthetic infection.

In 1999, Della Valle et al. [10] published a retrospective study of 64 patients (33 women and 31 men) who had undergone resection arthroplasty for periprosthetic infections and from whom FSs were obtained. The resection arthroplasties had been obtained a mean 40 months after arthroplasty and reimplantation occurred on average 19 weeks later. The threshold for suggesting infection was 10 PMNs in each of at least 5 HPF. Cases with fewer than 5 PMN in each of 5 HPF were interpreted as negative. None of the cases had more than 5 but less than 10 PMNs per HPF. As is common practice in pathology, microscopic fields represented areas of maximum neutrophil concentration, not the overall average of the entire section. Of the 64 patients, two had positive FSs, but one was negative on review of permanent sections. 61 of the 62 patients with negative FSs were also negative on review of permanent sections. Four patients were considered to be infected; the remaining 60 patients had negative cultures and histology. The results are summarized in Table I and indicate 25% sensitivity (the FS detected one of four persistent infections), 98% specificity, 50% positive predictive value (PPV), 95% negative predictive value (NPV) and 94% accuracy.

George et al. published two retrospective studies testing the use of FSs and permanent histology to diagnose infection at reimplantation. The first [11] sought to compare the diagnostic accuracy of FSs compared with the MSIS criteria of infection [12] and to further test the use of FS and MSIS criteria to predict clinical failure of reimplantation. The study identified 79 patients who had undergone two-stage revision for infected arthroplasty (38 knees and 41 hips) and had adequate records to assess MSIS criteria, had FS results and minimum 1-year follow-up. Patients had undergone the second step of the two-stage procedure after at least six weeks of antibiotics, and intraoperative samples at the time of reimplantation had been obtained for histologic and microbiologic evaluation. There were 48 men and 31 women. The threshold for interpreting a FS as supporting infection included 5 or more PMNs in 3 or more, 400X high power fields (based on fields with maximum PMN concentration). Note that this threshold requires fewer fields than commonly recommended, so might be expected to have greater sensitivity but less specificity than if 5 or more HPF were required. The FS results were compared to the reference standard, which for this part of the study was the based on the MSIS criteria. The results showed sensitivity of 56%, specificity of 94%, PPV of 50%, NPV of 94% and 90% accuracy (Table I).

Recognizing that rheumatoid arthritis might complicate the interpretation of serologic and other tests for infection at reimplantation, George and co-authors also reviewed the utility of Fss and permanent histology to diagnose infection at reimplantation in patients with an underlying inflammatory arthropathy [13]. They identified 47 revisions (39 patients) with confirmed inflammatory arthropathy, and compared the results of FS interpretation, and interpretation of corresponding permanent sections with the presence or absence of persistent infection as defined by the MSIS criteria at the planned second stage re-implantation. The threshold for positive histology was the same as in their previous study: 5 or more PMN in at least 3 HPF. The results of FS showed sensitivity of 56%, specificity of 95%, PPV of 73%, NPV of 97% and 87% accuracy. Of the 120 specimens analyzed by frozen and permanent sections, there were only four discrepancies. In each, the permanent section was interpreted as positive (infected) while the FS had been interpreted as negative, although not all of these were clinically relevant because some cases had other positive Fss. Ultimately the permanent sections had two false positive results and one false negative, while the FSs had two false positives and four false negatives. Therefore, the results of permanent sections were sensitivity of 89%, specificity of 94%, PPV of 80%, NPV of 97% and accuracy of 94% (Table I).

Although reported results are variable, most studies have indicated that the interpretation of a FS at revision arthroplasty has good NPV (i.e., absent neutrophils supports the absence of infection) [10], but that observation is dependent in part on sampling. In 2010, a Practice Guidelines Committee of the American Academy of Orthopaedic Surgeons (AAOS) found adequate high-quality published literature to support either of two diagnostic thresholds: 5 neutrophils in each of 5 HPFs (of maximum tissue concentration), or 10 neutrophils in each of 5HPFs [14]. A lower threshold for neutrophil concentration would be expected to be associated with increased sensitivity and lower specificity (increased false positive diagnoses [15]. Although most studies have shown the sensitivity of the two thresholds to be equivalent, some studies have reported slightly higher specificity if 10 neutrophils are required rather than 5 [16]. Recognizing that no test has perfect specificity and sensitivity, the

clinical importance of recognizing periprosthetic infection is high enough that some surgeons prefer maximizing sensitivity even at a slight cost of specificity. For example, Kwiecen et al. [4] recently reported sensitivity of 73.7% and specificity of 98.8% for a FS obtained at hip and knee arthroplasty using a threshold of 5 neutrophils in only 3 or more HRFs (the same threshold used in both studies by George et al. described above).

As noted above, the thresholds used to support the presence or absence of periprosthetic infection have been reported mostly from specimens obtained at intended primary revision arthroplasty. Patients with known periprosthetic infection are often treated with the two-stage procedure and it is thought that the surgery and presence of an antibiotic-containing spacer may alter the results of tests commonly used to diagnose infection, including serologic markers, joint aspiration with cell count, microbiologic cultures and possibly histology [2,17,18]. Although few published studies have included enough information to document sensitivity and specificity of different diagnostic thresholds for recognizing persistent infection at the second-stage of a two-stage operation for known infection, the results summarized here show similar values as those reported for FSs obtained at primary arthroplasty. Additional studies, including the use of special stains and rapid molecular tests are needed to help document either persistent infection or adequate resolution of the infection at the time of reimplantation.

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QUESTION 8: Should patients with periprosthetic joint infections (PJIs) caused by Mycobacterium tuberculosis (TB) undergo the typical two-week antimicrobial holiday prior to reimplantation?

RECOMMENDATION: There is no evidence supporting the two-week antimicrobial holiday before reimplantation. Patients with PJIs caused by TB do not need to have the two-week drug holiday.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 88%, Disagree: 6%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

TB is a rare cause of PJIs for which management is not clearly standardized [1,2]. This may be due to the little clinical suspicion and the difficulty in diagnosing this entity [3]. Literature reflects this infrequency with very few publications, the majority being case reports [2,4–14]. McCullough et al. [14] were the first to describe a prosthetic joint involvement due to TB. They hypothesized that this occurred during a bacteremic state following reactivation of latent tuberculosis. This and other reports have shown infection control can be achieved after surgical and pharmacological treatment although no conclusions can be made as to formal and standardization of treatment.

It is important to note that in the majority of publications, treatment is mainly focused on anti-TB chemotherapy associated with surgical intervention with or without removal of the prosthesis. Surgical treatment has been seen to be controversial and sometimes not performed [9]. Pharmacological management has been similar to that administered in extra-articular TB involvement. The literature contains only one systematic review, which included 15 patients, all of whom received 2- to 4-anti-TB chemotherapy agents (rifampin (RMP), isoniazid (INH), ethambutol (EMB) and pyrazinamide (PZA)) for at least six months (range 6 to 24 months) after diagnosis [7]. Thirty-three percent of patients (5 of 15) underwent surgical treatment including debridement and retention of the arthroplasty, while 20% (3 of 15) underwent staged revision arthroplasty, for which the anti-TB chemotherapy was continued at the time to reimplantation [10,11]. According to the latest publication which also included 66 patients, medical treatment with anti-TB chemotherapy varied from 4 to 39 months, as well as in type and number of drugs [13]. However, 56.1% of patients (37 of 66) received at least 12-month treatment. Surgical treatment ranged from debridement 17% (11 of 66), debridement & polyethylene exchange 8% (5 of 66), two-stage exchange 23% (15 of 66) to removal of prosthesis followed by arthrodesis 33% (22 of 66).

The anti-TB chemotherapy, along with surgical intervention, seems to be necessary for management of PJI caused by TB. The ideal duration of antibiotic treatment for these patients is not known, but most believe that at least four months of treatment should be instituted for patients with TB PJI. In addition, it is critical to ensure that patients with PJI caused by TB have no extra-articular nidus for infection. Given the fact that TB PJI could be considered a chronic condition, we consider that any strategy towards assuring infection control or eradication should be attempted.

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Pathogen Factors

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QUESTION 1: Does the virulence (low or high) of the infecting organism affect the treatment of acute hematogenous or chronic periprosthetic joint infections (PJIs)?

RECOMMENDATION: There is currently no evidence showing that the virulence of an infecting organism affects the treatment of acute hematogenous or chronic PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 69%, Disagree: 27%, Abstain: 4% (Super Majority, Weak Consensus)

RATIONALE

Pathogenicity is the ability of an agent to cause disease. The degree to which a pathogenic microorganism can cause an infectious disease is determined by its virulence. Several factors determine the virulence of bacteria, such as the bacterial capsule, presence of adhesin proteins, degradative enzymes, toxins and mechanisms for escaping elimination by host defenses (e.g., intracellular invasion and survival or production of biofilm). In addition, the host susceptibility to an infection also depends on its immune status and the presence of foreign material [1]. The type of virulence factor(s) expressed participate in the clinical presentation of disease. In general, microorganisms that are considered highly virulent tend to cause acute infections (e.g., *Staphylococcus aureus*, streptococci or gram-negative bacilli (GNB)) [2]. In contrast, pathogens with lower virulency are associated with chronic infections (e.g., *Cutibacterium acnes* (*C. acnes*), *Staphylococcus epidermidis* and other coagulase negative staphylococci (CoNS)) [2]. However, whether all virulence factors of a bacterium become expressed and to which degree, greatly depends upon the presence of specific environmental stimuli [3]. For this reason, we will address this question in two ways; 1) we evaluated whether the difference in virulency between different microorganisms (e.g., classically highly virulent microorganisms versus low virulence microorganisms) affect treatment outcome, and 2) we evaluated whether the degree of virulency factors expressed within one species affect treatment outcome.

Degree of Virulency between Different Microorganisms and its Relation to Outcome

A PubMed search was performed for late acute/hematogenous PJIs and chronic PJIs in relation to treatment outcome. All relevant articles were screened for inclusion and references were checked for additional articles. The total number of patients was counted in both groups and a success rate for all patients was calculated (Table 1) [4–19]. For late acute PJIs, 16 studies were included. Of 948 patients, the success rate with a debridement, antibiotics and implant retention (DAIR) procedure was 56% (range 35 to 94%). For chronic PJIs, one meta-analysis (including 62 studies) and 6 published studies thereafter were included [19–25]. Of 4,570 patients with chronic PJIs, treatment success rate was found to be 90% (range 87 - 100%) with one-stage or two-stage exchange procedures.

The outcome of acute and chronic infections is influenced by many factors, with the greatest difference being the surgical strategy used for acute versus chronic PJI—exchange versus no exchange of the prosthesis respectively. Due to the heterogeneity in treatment methods, it is not possible to conclude whether the worse outcomes observed in acute infections are due to the virulence of the bacteria. There are few studies that evaluate high versus low virulence microorganisms using the same surgical approach. Fink et al. studied 39 patients with early PJIs and 28 patients with acute hematogenous infections all of which were treated with DAIR and followed for a minimum of two years in order to investigate the success rate in infection eradication [27]. There was no difference in outcomes between infection caused by higher virulence pathogens (*S. aureus*, Streptococci, Enterococci, GNB) when compared to lesser virulence pathogens (CoNS and anaerobes such as *C. acnes*) [27].

Other authors have also compared the outcomes between *S. aureus* and CoNS PJIs. One study retrospectively examined chronic PJIs treated with suppressive antibiotic therapy [28], while another investigated the outcome of *S. aureus* PJIs versus CoNS PJIs treated with one- or two-stage revision [29]. Acute hematogenous and early PJI treated with DAIR and chronic knee PJI treated with different surgical modalities has also been examined in the literature. None of these studies found a significant difference in success rate after a minimum follow-up of 3 to 24 months [4,5,13–16]. Some authors have even described a worse outcome in patients with PJI caused by CoNS [4]. These findings suggest that virulence is not a risk factor for worse outcomes in PJI.

There are some observational studies that propose that *Staphylococcus* species are associated with recurrence or persistence of infection, due to the high capacity to form biofilms observed within this genus [30–32]. Others have suggested that *S. aureus* in particular is associated with a worse outcome than other microorganisms in general after DAIR [5,6,33,34] as well as after two-stage revision [35]. However, other studies do not observe any significant differences in outcomes of staphylococcal infections in general [36][37][38].

Degree of Virulence within the Same Species and its Relation to Outcome

Environmental stimuli play a large role in the phenotypic expression of virulence factors [3]. For example, it has been demonstrated that the amount of magnesium present in the environment of *S. aureus* determines the down or up regulation of specific virulence genes [15]. The resulting phenotypes have been shown

TABLE 1. Late acute/hematogenous PJI treated with DAIR

Article, Year	N	Success Rate	Comments
Wouthuyzen-Bakker 2018 [26]	340	55%	Unpublished data
Lora-Tamayo 2017 [7]	242	59%	Only streptococci
Akgün 2017 [8]	16	69%	Only streptococci
Tande 2016 [9]	35	74%	Only *S. aureus* bacteremia, 2y survival 62%
He 2016 [10]	11	82%	
Koh 2015 [11]	20	55%	
Holmberg2015 [13]	12	75%	
Puhto 2015 [12]	35	46%	
Koningsberg 2014 [5]	42	76%	
Geurts 2013 [14]	6	83%	
Lora-Tamayo 2013 [15]	52	35%	Only Staphylococci
Kuiper 2013 [4]	32	59%	
Rodriguez 2010 [16]	50	48%	
Byren 2009 [6]	12	83%	Only hips
Giulieri 2004 [17]	27	78%	
Everts 2004 [18]	16	94%	Only streptococci, only 1 patient had formal microbiological cure
TOTAL	**948**	**56%**	

TABLE 2. Chronic PJI treated with One-stage or Two-stage Exchange

Article, Year	N	Success Rate	Comments
Beswick 2014 [19]	4,197	90%	Meta-analysis comprising 62 studies with one-or two-stage exchange. Subanalysis of 11 studies with 1225 patients and only one-stage: success 91.4%
Singer2012 [21]	63	95%	Only 1st. exchange for TKA
Jenny 2013 [22]	47	87%	Only 1st. exchange for TKA
Haddad 2015 [23]	28	100%	Only 1st. exchange for TKA
Tibrewal 2014 [24]	50	98%	Only 1st. exchange for TKA
Zahar2016 [20]	70	93%	Only 1st. exchange for TKA
Gooding 2011 [25]	115	88%	2-step exchange for TKA
TOTAL	**4570**	**90%**	

to be associated with different infection outcomes in a murine model [15]. In addition, there is much debate over which virulence determinants of *S. aureus* are primarily responsible for infection severity in osteomyelitis [4,14,16]. Although some studies identified virulence determinants or bacterial strains involved in bone and joint infections [6,13,16,17], few evaluated whether the presence or absence of these virulence factors in PJI determine treatment outcome [6,17,18].

The literature search revealed three studies that examined the virulence within one species in relation to clinical outcome [4,15,16]. Tande et al. evaluated the outcome of PJIs caused by staphylococcal small colony variants (SCV), a phenotype that has been associated with intracellular persistence and biofilm formation [28]. Despite the general hypothesis that this phenotype is responsible for persistent and relapsing infections, treatment failure was 23.7% in staphylococcal PJIs caused by SCV compared to 30.7% failure in staphylococcal PJI with a normal phenotype ($p = 0.51$) resulting in a hazard ratio of 0.78 (confidence interval (CI), 0.36-1.69) [28]. The second study performed by Post et al. observed a clear relation between the degree of biofilm formation of *S. epidermidis* strains and clinical outcome in 104 patients with orthopaedic device related infections [39]. Weak biofilm formation was associated with a cure rate of 82%, while the formation of a strong biofilm was associated with a cure rate of 66.7% [39]. This difference however was not statistically significant. Strong biofilm formers were primarily observed to possess the of *icaA* gene (intracellular adhesion protein associated with biofilm formation) but the presence or absence of the gene itself was not related to clinical outcome [39]. In contrast, the presence of the gene *bhp* (cell-wall associated biofilm gene) was related to clinical failure, but only in infections of the lower extremity ($p = 0.023$) [39]. Morgenstern et al. conducted a similar study, however they found no statistically significant relationship between *S epidermidis* biofilm forming capabilities and cure rate ($p = 0.076$) [40].

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QUESTION 2: Is there a difference in the treatment outcome for periprosthetic joint infections (PJIs) caused by a single organism and a polymicrobial PJI?

RECOMMENDATION: Polymicrobial PJIs demonstrate inferior treatment outcomes when compared to monomicrobial PJIs. This finding is true for both patients treated with irrigation and debridement and two-stage exchange arthroplasty.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 97%, Disagree: 3%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

PJIs are not uncommon with a reported rate between 6 and 37% [1–4]. Although common organisms such as *Staphylococcus aureus* are commonly isolated in these infections, more virulent organisms such as Enterococcus species, gram-negative bacilli, methicillin-resistant *Staphylococcus aureus* (MRSA) and anaerobic bacteria are more commonly associated with polymicrobial rather than monomicrobial infections [5]. Despite the relative frequency of polymicrobial PJI, there is minimal literature regarding treatment outcomes of polymicrobial PJIs and how they compare to monomicrobial PJIs.

The literature demonstrates that polymicrobial PJIs have inferior outcomes when compared to monomicrobial PJIs. Tan et al. demonstrated that patients with polymicrobial PJI had a higher failure rate (50.5%) compared with monomicrobial (31.5%) and a higher rate of amputation (odds ratio (OR) 3.80, 95% confidence interval (CI), 1.34-10.80), arthrodesis (OR 11.06, 95% CI, 1.27-96.00), and mortality (OR 7.88, 95% CI, 1.60-38.67) compared with patients with monomicrobial PJI [6]. Similarly, Wimmer *et al.* demonstrated that the infection free rate after two years was 67.6 % for polymicrobial infections vs. 87.5 % for monomicrobial infections in a series of 77 polymicrobial PJIs [7]. Furthermore, Marculescu *et al.* demonstrated that the two-year cumulative probability of success of polymicrobial PJIs was 63.8% (95% CI, 43.8%–80.5%) and of monomicrobial PJIs was 72.8% (95% CI, 63%–80.9%). However, this difference was not significant.

The outcomes appear to be poor for polymicrobial PJI regardless of surgical treatment. Tan *et al.* demonstrated that the infection free survivorship for polymicrobial PJI was 55.4%, 49.3% and 49.3% for the two-stage exchanges and 43.2, 43.2 and 38.4% for irrigation and debridement (I&D) at 2, 5 and 10 years [6]. Although this result was not statistically significant, there was a trend towards higher treatment success (p = 0.164) for two-stage exchange arthroplasty. In Marculescu et al., the 2-year survival free of treatment failure for polymicrobial PJIs was 77.7% and 52.7% compared to 83.9 and 54% for monomicrobial PJI for, two-stage exchange arthroplasty and I&D, respectively. This rate was higher but not, statistically significantly different than of polymicrobial PJI treated with similar surgical modalities (p = 0.24 and p = 0.64) [5]. Bozhkova et al. also revealed that treatment success after the first stage of the two-stage procedure was considerably higher (74.8 %, $n = 101$) in patients with monomicrobial infection, compared to only 27.8 % ($n = 15$) in the polymicrobial group ($p < 0.0001$). [8] Furthermore, they found that gram negative PJIs in polymicrobial PJI were associated with failure as the proportion of polymicrobial PJI caused by gram-negative pathogens was 61.5 % in patients with recurrent infection and only 26.7 % in patients with treatment success (p = 0.03). According to data of Tornero et al., for I&D and retention of the prosthesis polymicrobial infection was significantly associated with failure in the global cohort (59.3% vs. 40.7%, p = 0.036) [9]. Only one study did not show the difference between outcome of polymicrobial and monomicrobial PJI [10]. However, this can be explained by insufficient number of PJI cases (only 15 cases) and pathogen properties (*Cutibacterium acnes* (*C. acnes*) in isolation or together with coagulase-negative staphylococci).

There are several explanations for the increased rate of failure in patients with polymicrobial PJIs. One factor is that drainage and the presence of a soft tissue defect have been found to be associated with polymicrobial PJIs [5,6]. Another is that polymicrobial PJIs are associated with organisms that are difficult to treat such as enterococcus and gram negatives [5,6,11] that have been associated with worse outcomes [12,13]. In addition, several studies have demonstrated that patients with polymicrobial PJIs have increased comorbidities and are older than patients with monomicrobial PJIs [5,6], which likely affects their ability to eradicate an infection.

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QUESTION 3: Is there a difference in the type of pathogens that can cause surgical site infections/periprosthetic joint infections (SSIs/PJIs) between hip and knee arthroplasty?

RECOMMENDATION: There is limited evidence to support a difference in the organism profile causing SSIs and PJIs between hip and knee arthroplasty. Isolated studies have reported an increased prevalence of *Streptococcal* and culture-negative PJI around the knee, whereas, *Staphylococcal, Enterococcal, Pseudomonal* PJIs may be more prevalent around the hip. Further work regarding the different flora in these respective body regions is needed, as it may determine antibiotic selection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 4%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Several studies have investigated the profile of organisms causing SSI and PJI following orthopaedic procedures with varying results. *Staphylococci* species are the most commonly isolated agents in orthopaedic prosthetic infections. According to recent literature, these pathogens are the primary source of up to 72% of infections [5–8]. Bacterial resistance has become a significant problem with certain studies reporting up to 27% of PJI are caused by methicillin-resistant organisms [9,10]. The prevalence of resistance also appears to be rising [11].

The published literature depicts *Staphylococcus aureus* (*S. aureus*) as the leading cause of PJI after total joint arthroplasty (TJA) [7,12,13]. A 14-year study evaluating the microbiological profile of PJI after two-stage revision from 1998-2011 found increased infection rates of methicillin-resistant *S.aureus* (MRSA), *Cutibacterium acnes* (*C. acnes*) and *Streptococcus viridans* (*S. viridans*) with no change in gram-negative, gram-positive or fungal infections [14]. Another study investigating 121 patients diagnosed with PJI after total knee arthroplasty (TKA) identified an increase in the prevalence of coagulase-negative *Staphylococcus* (CoNS) between 1994 and 2008, while *S. aureus* appeared to decrease [15]. A separate study conducted by Uçkay et al. evaluated resistance in CoNS orthopaedic infection over a 13-year period and did not identify any change in methicillin-resistance rates associated with CoNS [16].

Aggarwal et al. identified two different organism profiles when comparing 772 cases of PJI from the Rothman Institute in the United States (US) to 898 cases at HELIOS ENDO-Klinik, Hamburg in Europe [12]. The center in Europe had fewer *S.aureus* infections (13.0% vs. 31.0%), but more CoNS PJI than the US site (39.3 vs. 20.2%). There was also a significantly higher incidence of MRSA at the US center (48.1 vs. 12.8%; $p<0.0001$). However, there appears to be conflicting evidence regarding increasing prevalence of resistance in PJI [11].

The incidence of PJI affecting TKA versus total hip arthroplasty (THA) has been estimated at 1-3% and 0.3-2%, respectively [12–14]. Several studies have examined the organism profile causing PJI after arthroplasty, but few have identified any significant difference in profile between hip and knee arthroplasty.

Pulido et al. noted a higher rate of PJI in patients undergoing TKA (1.1%; 48 of 4185) compared to THA (0.3%; 15 of 5060; $p<0.0001$) [13]. A 14-year study identified a linear increase in MRSA, *S.viridans*, and *C.acnes* causing PJI after arthroplasty from 1998 to 2011. However, they identified no difference between organisms causing PJI in TKA and THA ($p> 0.05$) [14]. *Enterococcus* was found in the majority of THA (68%), but was not considered significant after a Bonferroni correction was performed comparing THA and TKA [14].

In a large multi-institutional study evaluating the organism profile causing PJI at two different academic centers, it was found that knees had more culture-negative infections at one of the two centers compared to hips. However, there were no other significant differences in organism profile when comparing hips and knees [12]. Drago et al. evaluated the organism profile and antibiotic susceptibilities of 429 patients diagnosed with PJI from 2013 to 2015 including 229 knee and 200 hip infections. Again, the authors found no difference in pathogen profile between hips and knees. *Staphylococci* were still the predominant organism affecting hips and knees followed by *Enterobacteriaceae* and *C.acnes*. However, methicillin resistance in CoNS was twice as prevalent around the knee versus the hip. Increased resistance to glycopeptides and fluoroquinolones was also observed around the knee in comparison to the hip [17]. Future

studies should aim to further investigate these potential differences in the organism and resistance profiles in hips and knees diagnosed with SSI and PJI.

Groff *et al.* recently examined 1,214 PJI cases (501 hips and 713 knees) over a 17-year timeframe and found significant differences in pathogens causing PJI in the hip and the knee. A higher incidence of *Streptococcal* species (odds ratio (OR) 1.82, 95% confidence interval (CI), 1.23-2.67) and culture-negative PJI (OR 1.53, 95% CI, 1.12-2.09) were identified in TKA compared to THA. In contrast, *Pseudomonas* (OR 2.123, 95% CI, 1.04-4.34), *Enterococcus* (OR 1.72, 95% CI, 1.03-2.86), resistant species (OR 1.64, 95% CI, 1.19-2.25), *Staphylococcus aureus* (OR 1.40, 95% CI, 1.11-1.77) and gram-positive (OR1.37, 95% CI, 1.05-1.78) organisms were more prevalent in hips. The authors suggested that the higher rates of urogenital-associated pathogens causing PJI in hips may have been related to the close proximity of the incision to the flexural creases and the groin region.

Although most studies have not demonstrated a definitive difference in organism profile between hips and knees, some have identified differences in virulence patterns, culture-negative rates, urogenital and fecal bacteria, as well as the overall rates of PJI in bilateral compared to unilateral TKA [12–14,17]. It is important to further delineate the differences in organism profile at these anatomic sites in order to establish adequate protocols and select antimicrobials accordingly, that may account for potential differences in the pathogenic flora and mitigate the risk of SSI/PJI.

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QUESTION 4: Is there a difference in the organism profile that causes periprosthetic joint infections (PJIs) in different countries?

RECOMMENDATION: Yes, there is a difference in the organism profile causing PJIs in different countries and regions of this world. There seems to be a higher incidence of PJI caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in the United States and Australia compared to Europe.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 97%, Disagree: 1%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

General strategies to prevent occurrence of PJIs have become more relevant over the last few years. As one recommendation of the International Consensus Meeting on Periprosthetic Joint Infection in 2013, surgical antibiotic prophylaxis with either single or 24-hour dose of cephalosporin should be performed. However, antibiotics (prophylactic and therapeutic) should be selected to cover the most frequently encountered pathogens, which might vary regionally, nationally and internationally (and could be affected as well by other factors) and not simply be administered empirically.

To date, several authors have described the bacterial incidence in isolated series of PJI with either single- or multicenter studies. However, the comparison of organism profiles causing PJI between countries or world regions has been evaluated by relatively few studies.

A study comparing organism profiles between PJI referral centers in the United States (US) (Rothman Institute) and Europe (HELIOS ENDO-Klinik) found that the percentage of MRSA pathogens was significantly higher in the US than in Europe [1]. In addi-

tion, a higher incidence of more virulent organisms was found in the US patient cohort in this study. Stefansdottir et al. and Phillips et al. in their study also found a higher incidence of coagulase-negative *Staphylococcus* (CoNS) and *Streptococcus* pathogens compared with *Staphylococcus. aureus* (*S. aureus*) within various European registries (United Kingdom (UK) and Sweden) [2,3].

Peel *et al.* [4] showed that causative pathogens in PJI differ significantly in Australia compared to other reported studies and geographic regions such as the US, Sweden and the UK. In particular, the rates of polymicrobial infections showed high differences (36 vs. 14 %), as did the isolation of MRSA (over 40 % of all cases), as compared to previous European and US reports.

Pakroo *et al.* [5] reported similar geographic variation in organisms causing spinal infections in patients presenting to a tertiary referral center in the UK. The epidemiology and antibiotic susceptibility of bacteria causing skin and soft tissue infections do show geographic variation (e.g., between US, Germany, Italy and Spain) differentiating between MRSA, methicillin-sensitive *Staphylococcus aureus* (MSSA) and CoNS pathogens [6]. Although these data which relate predominantly to general skin infections cannot be easily transferred to PJI, it has been well accepted that such local infections (at the time of surgery or after) subsequently might lead to PJI.

Furthermore, it has been shown that community-acquired soft tissue MRSA infections have a much higher incidence in the US compared to Europe [7]. While a large percentage of soft-tissue infections are caused by community-acquired MRSA in the US, the community-acquired MRSA cutaneous infection rate in Europe only accounts for between 1 and 3% of presenting wound infections [8].

Along with this geographic variability, Anthony *et al.* [9] found a seasonal variability of surgical site infection (SSI) in total knee arthroplasty (TKA) and total hip arthroplasty (THA), with seasonal increase of SSI between 30 and 19% in patients with TKA or THA procedures respectively in the summer months, suggesting the possibility that geographic temperature conditions might influence the incidence and etiology of PJI. This data was extracted from a US National Database.

Data from several multicenter, retrospective studies has demonstrated that the organisms causing PJI vary by country or region of the world. An increasing number of PJIs are being caused by more virulent and resistant organisms such as MRSA in the US and Australia. With the literature lacking large prospective studies, we assign a moderate recommendation.

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Fungal Periprosthetic joint infection

4.1. FUNGAL PERIPROSTHETIC JOINT INFECTION: DIAGNOSIS AND TREATMENT

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QUESTION 1: What is the optimal method to diagnose fungal periprosthetic joint infection (PJI)?

RECOMMENDATION: Diagnosis of fungal PJIs is established by incubating joint aspirations or tissue samples collected intraoperatively on specialized culture media. Furthermore, isolation of fungal species may take up to four weeks. However, given the shortcomings associated with the use of culture, alternative techniques capable of detecting fungi, such as molecular techniques, may be used as an adjunct.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 3%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

PJIs can be caused by an expanding number of infecting organisms. While the vast majority of these organisms are gram-positive cocci, atypical organisms such as fungi have also been shown to be associated with PJIs and present an even more difficult diagnostic challenge [1,2]. In the largest series published, 31 fungal PJIs presented with indolent onset of joint swelling and pain frequently without other systemic symptom or signs of infection [3]. In another series, about 50% of patients who had fungal PJIs had radiographic evidence of loosening [4] and could be misdiagnosed as aseptic loosening, especially for those having normal serum inflammatory markers [5]. Serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) joint fluid cell counts and bone scintigraphy have limited value for diagnosis of fungal PJIs [6–8]. While the aforementioned tests all help to establish the presence or absence of an infection, they provide no information regarding the identity of the infecting organism.

Perioperative cultures, such as aspirated synovial fluid, as well as intraoperative tissue and swab samples, have been considered diagnostic standards for fungal PJIs [3,4,10,11]. Unfortunately, culture has been shown to have sensitivity as low as 50%. Given that these studies were assessments of the overall accuracy of culture in diagnosing PJI and not fungal infections specifically, culture may even perform worse in the setting of fungal PJIs [12–16]. Fungi are notoriously difficult to isolate in culture due to several reasons. First, culturing fungi requires the use of specialized media, with various modifications needed in order to isolate different species of fungi [17]. The universal media for most fungi is Sabouraud dextrose brain heart infusion (BHI) agar or plain BHI agar [18]. A blood-containing media such as BHI agar with 10% sheep blood improves the sensitivity or recovery of dimorphic fungi. Special media are required for fastidious organisms, such as bird seed agar for *Cryptococcus neoformans*, chromogenic agar for Candida, dermatophytes' test medium for dermatophytes, and longchain fatty acid supplementation for *Malassezia furfur* [19]. Second, the traditional duration to culture slowly growing fungi requires four weeks or longer. A study of 3,036 fungal cultures showed that an incubation period of two weeks is sufficient for the detection of yeast or molds, whereas, a four-week incubation period is necessary for dermatophytes [18]. Given the potential for identifying a fungal organism up to a month following resection arthroplasty, more expeditious methods of pathogen identification are needed. The vast majority of techniques have focused on sequencing of the 16S segment, a highly conserved region of bacterial DNA that allows for identification of bacteria at the species level [15,20,21]. Thus, many of these techniques are unable to identify fungal organisms; however, sequencing of the Internal Transcribed Spacer segment, a fungal sequence analogous to the 16S segment [22,23], demonstrated a sensitivity of approximately 90%, with a turnaround time of a week, a massive improvement over culture [24].

In conclusion, culture remains the primary method for identification of fungal organisms in the diagnosis of PJIs. However, in light of the difficulties associated with isolation of fungal organisms, alternative techniques are needed. Techniques capable of detecting fungal organism, such as next generation sequencing (NGS), may be used as an adjunct in the diagnosis of fungal PJI.

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QUESTION 2: Should patients with periprosthetic joint infections (PJIs) caused by a fungus undergo the typical two-week antimicrobial holiday prior to reimplantation?

RECOMMENDATION: There is no conclusive evidence to support the use of an antimicrobial holiday period prior to reimplantation in case of fungal PJI treated with staged revision.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 5%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The review of the literature on fungal PJIs treated with staged revision shows only 8 retrospective cohort studies (level of evidence IV) and 13 case reports (level of evidence V) (Table 1). We have been able to find only 21 papers (104 patients) regarding fungal PJI treated with two-stage exchange arthroplasty. In 68 cases (from 14 different studies), a drug holiday of at least two weeks was applied before reimplantation. No drug holiday was prescribed in two cases. For the remaining 34 patients, there was no data available about this aspect. Candida spp. (especially *albicans* or *parapsilosis*) was the main causal agent. Most patients had at least six weeks of systemic antifungal treatment after first operation, in agreement with the 2013 Consensus Conference conclusions. Following reimplantation, antifungal agents were continued for from two weeks to six months in six studies (69 patients). The agent most frequently used was fluconazole. Among reviewed papers, most authors seem to prefer a drug holiday of two or more weeks before second surgical stage. This approach is consistent with the conclusion of the previous Consensus Conference in 2013. No study compares the results of the two different strategies.

In conclusion, antifungal therapy could be stopped before reimplantation but there is no high-quality evidence to support this opinion.

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TABLE 1. Retrospective cohort studies regarding the recommendation duration of systemic antifungal agents for fungal periprosthetic joint infection treated with two-stage exchange arthroplasty

Author	Year	N	Organism	Length of Anti-fungal Therapy	Length of Interstage	Drug Holiday	Outcome
Hennessy [1]	1996	1	*C. parapsilosis*	13 w	not known	not known	cured
Ramamohan [2]	2000	1	*C. glabrata*	6 w	6 w	0	cured
Yang [3]	2001	1	*C. parapsilosis*	10 w	3 m	2 w	cured
Baumann [4]	2001	1	*A. fumigatus*	6 w	8 w	2 w	cured
Phelan [5]	2002	10	Candida spp.	25 w (2-49)	6.7 m (8 days-17.7 m)	1.4 m	8 cured
Cutrona [6]	2002	1	*R. minuta*	not known	12m	not known	cured
Wyman [7]	2002	1	*C. tropicalis*	not known	not known	not known	cured
Azzam [8]	2009	31 (19 with two-stage)	*C. albicans* (20) *C. parapsilosis* (4) both above (3) *C. glabrata* (1) Aspergillus (1) Others (2)	6 w after RA 6 m after reimplantation	7 m (range 2-14)	≥2 w	9 cured/ 10 failed
Dutronc [9]	2010	7 (3 with two-stage)	*C. albicans* (4) *C. parapsilosis* (2) *C. guilliermondii* (1)	not known	not known	not known	1 cured/ 2 failed
Wu and Hsu [10]	2011	1	*C. albicans*	17 w after RA 6 m after reimplantation	6 m	7 w	cure
Yilmaz	2011	1	*A. fumigatus*	6 w	4 m	10 w	cure
Graw [11]	2010	2	*C. albicans*	12 w	not known	8 w- 1 y	failed
Hwang [12]	2012	28	*C. parapsilosis/albicans*	≥6 w after RA A maximum of 6 m after reimplantation	9.5 w (6-24)	not known	22 cured/ 4 failed
Anagnastakos [13]	2012	5	*C. albicans (2)* *C. lypolitica* *C. albicans+C. glabrata* *C. glabrata*	6 w	12.8 w (12-14)	6.8 w (6-8)	cured
Kuiper [14]	2013	8 (4 with two-stage)	*C. albicans* (6) *C. albicans* + *C. glabrata* *C. parapsilosis* (1)	8.75 w (1w-5mo)	6.5 m (4-14 m)	>8 w (8-50w)	2 cured/ 2 failed
Deelstra [15]	2013	1	*C.albicans*	not known	not known	no	cured
Ueng [16]	2013	8	Candida spp	14 m after RA (3-18 m) 2.5 m after reimplantaiton	not known	≥2 w	8 cured/ 1 deceased

Author	Year	N	Organism	Length of Anti-fungal Therapy	Length of Interstage	Drug Holiday	Outcome
Reddy [17]	2013	1	*C. tropicalis*	18	20 w	2 w	cured
Wang [18]	2015	5	Candida spp	8 w after RA (6-10) 2 w after reimplantation	6 m	>2 m	5 cured
Geng [19]	2016	8	*C. albicans* (3) Mould *C. freyschussii* Aspergillus spp *C. parapsilosis* *C. glabrata*	2.8 m after RA (1.5-6) 1m after reimplantation (1m-46 days)	4.3 m (3-7)	6 w (2w-10w)	7 cured
Sebastian [20]	2017	1	*C. tropicalis*	24 w	9 m	3 m	cure

RA, resection arthroplasty

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QUESTION 3: Can debridement, antibiotics and implant retention (DAIR) be used to treat acute fungal periprosthetic joint infections (PJIs)?

RECOMMENDATION: DAIR has a relatively high failure rate in fungal PJIs, especially for immunocompromised patients. DAIR should be reserved for patients with truly acute PJIs after an index arthroplasty and in healthy patients (Type A). If DAIR is performed for fungal PJIs, consideration should be given to anti-fungal suppression therapy.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 91%, Disagree: 5%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

PJIs caused by fungal pathogens are a rare occurrence accounting for <1% of all PJIs [1]. Surgical treatments for fungal PJIs include DAIR, one-stage exchange arthroplasty and two-stage exchange arthroplasty. The difficultly in the treatment of fungal PJIs can be attributed to the rarity of fungal PJIs that have confined our understanding of this infectious entity and the often-immunocompromised status of patients who develop these infections in the first place. Although some general agreements have been reached with recommendations proposed by the International Consensus Meeting (ICM) and Infectious Diseases Society of America (IDSA) [2,3], many issues related to fungal PJIs remain unresolved. The most optimal surgical option for patients with fungal PJIs, the dose and the type of antifungals to be added to the polymethyl methacrylate (PMMA) spacer, the optimal duration of systemic antifungal treatment and many other issues still remain unanswered.

In addition, despite offering a potential explanation above, the exact reason for the less optimal outcomes of treatment of fungal PJIs remains unknown. It is, however, known that patients with

fungal PJIs often have an immunocompromised condition, such as diabetes mellitus, rheumatoid arthritis and cancer, which may markedly contribute to the high failure rate of treatments [3]. In addition, the complexity of the fungal biofilm in having a highly heterogeneous structure in response to environmental conditions, such as differences in pH, oxygen availability and redox potential, could also contribute to the suboptimal outcomes of treatment [4].

Overall, DAIR has been reported to have a relatively high failure rate in patients with PJIs caused by resistant organisms and poor hosts. DAIR as a surgical option for patients with fungal PJIs is questionable [5], and a study published in the *New England Journal of Medicine* listed fungal PJIs as a contraindication for DAIR [6]. A search of Medline, PubMed, Embase, Web of Science and Medscape revealed no reports in the setting of DAIR for acute fungal PJIs. The review of the English literature from 1979 to 2018 identified 22 fungal PJIs undergoing DAIR [7–19]. An overall high failure rate (82%, 18 of 22) was reported for these patients. Additionally, one study by Azzam et al. demonstrated a 100% failure rate for seven patients in their cohort undergoing DAIR [16]. Among the seven patients who failed, five needed resection arthroplasty and two needed chronic suppression with oral fluconazole [16]. Furthermore, Badrul et al. reported a fungal PJI case treated with debridement and oral fluconazole for a year. But, the infection was never totally cured and a secondary infection with methicillin-resistant *Staphylococcus aureus* (MRSA) developed [14]. Fabry et al. also reported a failure in a patient who underwent two debridements and an eight-month oral antifungal therapy regimen [15]. However, a few case reports demonstrated successful results at a minimum follow-up of two years and all of them required a six-months to one-year antifungal agent treatment after irrigation and debridement alone [9,11,12,18,19].

Given the fact that literature is not definitive on this issue and based on the available reports, we recommend that DAIR for fungal PJIs should be limited to those with early presentation, good soft tissue coverage, well-fixed implants and are healthy patients (Host type A). If DAIR is performed for patients with fungal PJIs, long-term suppression (six months or longer) with antifungal agents should also be considered.

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QUESTION 4: Which antifungals, route of administration and duration of treatment should be utilized to treat fungal periprosthetic joint infections (PJIs)?

RECOMMENDATION: Fluconazole, by both oral and intravenous routes, is currently the treatment of choice for PJIs due to susceptible fungi, including the *Candida* species which are responsible for the majority of fungal PJI cases. Amphotericin B lipid formulations or echinocandins given intravenously are secondary considerations, but may be less well tolerated. Culture data including antifungal susceptibilities should be used to guide therapy. Two-stage revision is currently the standard of care. Antifungal treatment should be administered during the spacer interval with a minimum treatment duration of six weeks. Following revision, treatment with oral fluconazole (400mg daily) should be continued for three to six months, if tolerated.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 3%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Fungal PJIs are uncommon, accounting for approximately 1% of PJIs [1,2]. *Candida* species, in particular *Candida albicans*, are by far the most common pathogen [1,3]. Concomitant bacterial infection may occur in up to 20% of cases [4]. Risk factors for fungal

PJIs include immunosuppression, systemic disease and extended antimicrobial therapy [5]. *Candida* infections are associated with biofilm formation which plays a key role in the development of PJIs [5,6]. Given the infrequency of fungal PJIs, there are no standard guidelines regarding treatment. The current literature contains retrospective case series and case reports. There are no randomized clinical trials, prospective cohort studies or case-control studies to guide therapeutic decisions.

Candida PJI has been treated successfully with antifungal therapy alone in several case reports [7,8]. Two-stage revision, however, is regarded to be the current standard of care for the surgical management of fungal PJI as high failure rates have been reported with primary debridement. Debridement, antibiotics and implant retention (DAIR), as well as single-stage revision, were shown to have a failure rate of up to 50% [1,2,9,10]. A two-stage revision with interval antibiotic therapy is consistent with the Infectious Diseases Society of America (IDSA) guidelines for bacterial PJI [11]. The role of antifungal eluting bone cement is controversial. Fluconazole is not currently available as a sterile powder. Both amphotericin B and voriconazole can be added to cement. Data show that voriconazole is more effectively released than amphotericin B and that it achieves and maintains high intra-articular concentrations [12–17].

Systemic antifungal therapy is administered during the spacer interval. Treatment options include fluconazole (400mg (6mg/kg) PO/IV daily), an echinocandin (caspofungin 50 to 70mg IV daily, micafungin 100mg IV daily or anidulafungin 100mg IV daily) or lipid formulation amphotericin B (3-5 mg/kg IV daily) [18]. The minimum duration of antifungal therapy after resection should be 6 weeks with up to 12 weeks considered. Revision surgery should be delayed three to six months in most cases [18,19]. Antifungal therapy should be discontinued and aspiration of the joint space should be culture-negative prior to revision. Following revision, fluconazole (200mg to 400mg PO daily) should be continued for a minimum of six weeks with up to six months or longer considered [2,5,18,20].

The incidence of fungal PJI is expected to rise given the increasing number of joint arthroplasties performed each year [21]. While specific guidelines for the management of fungal PJI have yet to be established, important considerations in management include confirmation of microbiologic diagnosis including antifungal susceptibility testing of fungal isolates, surgical options with two-stage exchange arthroplasty currently favored, the use of antifungal eluting cement and long-term systemic antifungal therapy.

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Treatment

5.1. TREATMENT: ALGORITHM

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QUESTION 1: Should early postoperative infection and acute hematogenous infection be treated and managed differently?

RECOMMENDATION: There is no evidence to support the notion that early postoperative infection and acute hematogenous infection should be treated differently as long as the onset of symptoms is <4 weeks (favorable <7 days), implants are well-fixed, no sinus tract exists and the isolated infecting organism is sensitive to an antimicrobial agent.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 94%, Disagree: 5%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Early postoperative infection is usually defined as infection occurring within three weeks of index arthroplasty, although some authorities state that any infection within three months (90 days) of the index arthroplasty should be considered acute [1]. Hematogenous infections associated with a remote source are often classified as late infections, which can occur one to two years after arthroplasty [2]. Acute hematogenous infection is defined as infections with no more than three weeks of symptoms [3]. According to the Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), patients who have a well-fixed, functioning prosthesis without a sinus tract, infection occurring within 30 days of index arthroplasty or <3 weeks of onset of infectious symptoms and having an organism susceptible to oral antimicrobial agents, should be candidates for debridement antibiotcs and implant retention (DAIR) [4]. The International Consensus Meeting (ICM) 2013 also proposed that DAIR should be considered in patients with infection occurring within three months of the index arthroplasty, with less than three weeks of symptoms in early postoperative infections and those with symptoms less than three weeks in late hematogenous infection [3]. When these criteria are met, DAIR is a reasonable option for early postoperative or acute hematogenous infection. However, because of the relatively high failure rate of DAIR in some reports and the fact that mature biofilm on an implant surface forms within a few days, some studies have suggested that DAIR should be restricted to patients with less than five days of infection symptoms [5].

One prospective study demonstrated that 52% of acute hematogenous infections failed at two-year follow-up following DAIR [6]. Treatment failure rates were 57.8% in staphylococcal infection, 14.3% in streptococcal infections and no failures were seen in gram-negative PJI [6]. A second comparative study reported that the success rates after DAIR in hip and knee PJI may be significantly increased if treatment was initiated within two days of symptoms [7]. In the latter study, DAIR showed overall success rate of 82.1% for early infections and 57.1% for acute hematogenous infections. Patients with acute hematogenous infections had an eight-fold higher chance of failure. Given the higher failure rate in the acute hematogenous group, the authors suggested that treatment parameters for these infections required additional studies with higher patient numbers [7]. A recent study evaluating the outcome of DAIR showed no statistically significantly different treatment outcome between early postoperative infection (15%) versus acute hematogenous infection (21%) [8]. Modular components were exchanged in only 70% of the included patients in the latter study. Systemic host grade A (McPherson classification) was a strong predictor of treatment success [8].

Several systematic reviews suggest that interventions in both early postoperative and acute hematogenous infections should be timely and aggressive (with exchange of modular parts), as each additional day of waiting lowers the odds for a successful outcome [9–12]. A recent meta-analysis reported the significant determinants of successful outcome following DAIR [12]. Time from onset of symptoms or index arthroplasty (< 7 days) and the exchange of modular components were the most significant factors influencing outcome. In the latter meta-analysis, the authors detected that the reported success of DAIR has increased since 2004 [12]. The exact reason for this improvement in outcome is not known but may relate to a publication in 2004 by Zimmerli et al. which established an algorithm for DAIR [10]. The algorithm may have encouraged the orthopaedic community to change their indications for DAIR, attempt to optimize patients prior to DAIR by modifying risk factors for failure and possibly altering the administration of antimicrobial regimen.

Virulent organisms causing PJI are also predictors for treatment failure following DAIR, according to some studies. *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA) have been reported to result in a higher failure rate following DAIR when compared to gram-negative pathogens [9,13]. In addition, infections with methicillin-resistant *Staphylococcus epidermidis* (MRSE) and vancomycin-resistant enterococci (VRE) have been associated with inferior outcome following DAIR [9,10]. In contrast, in a study on early postoperative and acute hematogenous infections caused by *S. aureus*, this difference could not be shown [14].

Acute hematogenous infection might be a marker of poor general health as almost half of the patients in one study had some critical medical comorbidity that may have predisposed them to developing infection in the first instance [15]. Relative high mortality rates around 20% after 2 years has been reported for patients with acute hematogenous infections, which could be attributed to higher rates of systemic sepsis at presentation in this patient population [14,15].

In conclusion, DAIR is a viable option and a reasonable first therapeutic approach for patients with early postoperative and acute hematogenous infections. However, some studies have reported a high failure rate of this surgical treatment and a relatively high early mortality rates after DAIR for acute hematogenous infections compared to acute postoperative infections. These differences might be related to differences in the pathoetiology of these infections and the influence of the intrinsic host factors on the outcome. Therefore, studies focusing on improving treatment outcomes after acute hematogenous infections are desperately needed.

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QUESTION 2: Should operative treatment differ in patients with systemic sepsis in the setting of periprosthetic joint infection (PJI)?

RECOMMENDATION: Yes. Patients with systemic sepsis in the setting of PJI should have surgical bioburden reduction, either with implant retention or resection of components (if indicated and safe), along with concurrent anti-microbial therapy. Reimplantation should be delayed until sepsis is resolved.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 79%, Disagree: 19%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Infection of total joint arthroplasty is a known and devastating complication all surgeons seek to avoid. Despite best efforts, prosthetic joints can be seeded from local and systemic sources [1–9]. Although PJI usually presents without systemic signs of pyrexia, chills and other symptoms, occasional PJI may result in systemic sepsis when the blood culture may also be positive for infection. In the context of systemic sepsis, hematogenous spread is the definitive mechanism by which PJI develops in previously well patients. Orthopaedic infections appear to be caused by the same common group of bacterial pathogens. In this group, the majority are gram-positive cocci, namely, *Staphylococcus aureus* and *Staphylococcus epidermidis*. There is the ever-present threat of methicillin-resistant *Staphylococcus aureus* (MRSA) as a difficult PJI infection to remove. Moreover, the growing number of vancomycin-resistant enterococcus and other serious gram-negative bacteria are also a concern. Gram-negative bacteria are associated with more severe episodes of sepsis due to the production and release of lipopolysaccharides (endotoxin).

Highlighted across several studies is the concept of the arthroplasty surface acting as a unique microbial substratum [10]. Gallo et al. reported the affinity of *S. epidermidis* to attach to polyethylene surfaces as opposed to *S. aureus* preference for bare metal. In each of the papers examined by Gallo et al. the presence of biofilm on the wearing or corroded surfaces of the implants was a key factor in the bacterial resistance to host and antimicrobial attack. A paper referenced in the Gallo et al. review by Gristina [11], characterised the colonization of the prosthesis as a "race for the surface" [10]. This concept is apt at highlighting the need for pathogens to colonize, undeterred by local and host factors.

These concepts are of pivotal importance when examining the published material reviewed here in the context of the original question, "to evaluate whether operative treatment should differ in patients with systemic sepsis in the setting of prosthetic joint infection." As demonstrated in this review and supported by the significant cohort size, PJI can occur as a consequence of local or hematogenous colonization. Overall, severity of infection is higher with hematogenous spread [12–14], as is the difficulty in clearing the infection for subsequent implant revision. Osteomyelitis prior to implantation of prosthetic joints indicates increased risk as

reported by Jerry et al. [4]. The nearly 5-fold increase in recurrence rates seen in patients with prior bone infection serves as a significant warning to surgeons to adequately debride as much contaminated surface as is feasible to allow for control of infection and subsequent implantation.

Based on the articles included in this review, there is no evidence to suggest that the implantation of prosthetic joints during an episode of sepsis is advisable. Often, however, joint arthroplasty procedures will need to be performed to alleviate the tremendous pain associated with infective destruction of a joint surface. Each of the included studies recommended a staged approach to surgical management of PJI with the most common approach being two-staged revision. There is very limited evidence to support retention of implants if a curative outcome is the main objective of the treatment. Also, there is a lack of evidence to suggest initiating antibiotic therapy to counter the systemic sepsis before the first-stage revision surgery. Though, identification and eradication of clinically obvious secondary foci, like indwelling catheters and skin, soft tissue, respiratory and genito-urinary infections, could be of vital importance for controlling the PJIs and preventing subsequent relapse. Therefore, like PJIs without systemic sepsis, a combination of effective debridement and concurrent intravenous antimicrobial therapy is the current best practice standard of care. The main limitation associated with the effective execution of this thorough and proven care strategy seems to be the accurate diagnosis of the complete clearance of infection to restore *aseptic* status to the patient.

It must be noted, as of the completion of this review, there are no studies that directly evaluate whether operative treatment should differ in patients with systemic sepsis in the setting of PJI. There are a number of closely related papers quoted above, but that is the limit of current knowledge. It is, however, our opinion that patients with systemic sepsis exhibiting constitutional symptoms are at serious risk and should be treated urgently. The best option of treatment is bioburden reduction which involves extensive soft tissue debridement and removal of infected prostheses.

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QUESTION 3: What should be done for patients with persistent wound drainage (PWD) after total joint arthroplasty? What are the indications for surgical intervention?

RECOMMENDATION: Management of draining wounds after total hip arthroplasty (THA) or total knee arthroplasty (TKA) consists of two main steps; nonoperative and operative. The nonoperative measures include: modification of venous thromboembolism (VTE) prophylaxis, nutritional supplementation, dressing measures (such as negative pressure wound therapy (NPWT)) and restriction of range of motion. If draining continues for more than seven days after implementing the nonoperative measures, operative interventions may be indicated – including irrigation and debridement, synovectomy and single-stage exchange. In certain situations, superficial wound washout may be indicated (Fig. 1).

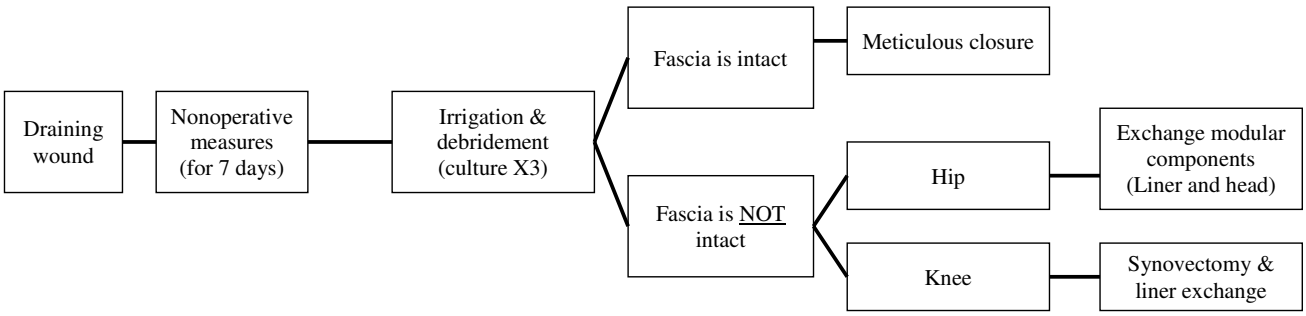

Figure 1. Management of draining wounds after total joint arthroplasty.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 89%, Disagree: 8%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Drainage after THA and TKA increases the risk of subsequent superficial or deep infection. Studies have shown that the risk of deep infection increases by 29% after TKA and 42% after THA with each additional day of drainage [1].

Definition

Persistent wound drainage (PWD) by definition is an area of drainage greater than 2 x 2cm on the incisional gauze that persists over 72 hours postoperatively [2]. Drainage can be due to hematoma, seroma, fat necrosis or defects in arthrotomy closure [3].

Nonoperative Measures

Ceasing anticoagulation agents: Anticoagulation agents for VTE prophylaxis have been shown to affect PWD after THA and TKA. Low molecular weight heparin (LMWH) leads to higher rates of prolonged wound drainage after THA and TKA compared to aspirin and warfarin [1]. Fondaparinux had fewer wound complications but no difference in infection after TKA compared to aspirin, LMWH or warfarin [4]. Dabigatran was found to have an increased rate of wound drainage and increased length of stay following TKA and THA [5]. Therefore, one of the first steps in patients with PWD is to cease the anticoagulation medications, if possible.

Negative pressure wound therapy: NPWT applied to closed incisions following TKA or THA has been shown to reduce the rate of superficial wound infection [6]. In patients undergoing primary total hip or knee arthroplasty, NPWT has been shown to reduce post-surgical wound exudate, number of dressing changes, a trend toward reduced length of stay and a trend toward reduced post-op surgical wound complications [7]. Using ultrasound to measure volume, NPWT has been shown to reduce the size of post-op seromas when compared to a standard dressing [8]. NPWT applied 3-4 days after THA for persistent drainage resulted in drainage resolution in 76% while 24% required further surgery [9]. As part of local wound care in the first 7 days of PWD, we recommend using incisional NPWT systems.

Nutrition: Malnourishment has several definitions. One of the most commonly used ones is: serum transferrin <200mg/dL, serum albumin <3.5g/dL or total lymphocyte count <1500/mm3. Poor nutritional status is associated with a significant (up to 5-fold) increase in risk of wound complications following THA and TKA [10–12]. Malnourished patients are more likely to fail nonoperative treatment (odds ratio (OR) 18.29), as well as surgical debridement (35% vs. 5%, p<0.0003) [3]. We strongly urge modifying the nutritional status of the patients prior to an elective arthroplasty procedure. In case of a PWD, postoperative nutritional supplements can help to improve the wound healing process.

Surgical Intervention

Surgical intervention for drainage should be considered after five to seven days of PWD [1–3]. Saleh et al. [2] conducted a 20-year surveillance study and concluded that patients with longer than five days of drainage have 12.7 times higher likelihood to develop surgical site infection in comparison with those who had less drainage time. Therefore, we recommend proceeding with surgical intervention if the PWD continues for more than seven days.

The first step of the surgical intervention is irrigation and debridement (I&D) and obtaining at least three intraoperative cultures. Irrigation is recommended to be performed with at least 9 liters of an irrigation solution, such as normal saline or an aqueous iodophor solution. At this point if the fascia is found to be intact, we recommend meticulous closure. However, if the fascia is not intact, modular components should be exchanged [1,3]. Studies have shown promising results with single I&D. Jaberi et al. [3] reported that in THA and TKA patients with PWD, drainage stopped in 76% of patients after single-stage I&D. The remaining 24% required subsequent treatments such as repeat I&D, removal of implant or long-term antibiotic administration.

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QUESTION 4: How should infected bilateral hip or knee arthroplasties be managed?

RECOMMENDATION: The optimal surgical treatment for infected bilateral hip or knee arthroplasties is unknown. While revising the components likely provides improved outcomes over limited debridement with component retention, data does not preferentially support either a single-stage or two-stage exchange revision arthroplasty

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 83%, Disagree: 11%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Infected bilateral hip or knee arthroplasties present a rare treatment dilemma for both the patient and surgeon. The literature on this topic is limited, however, with only two small case series and at least nine case reports describing multiple simultaneous periprosthetic joint infections (PJIs) [1–17]. Treatment options include debridement with component retention, single-stage revision and two-stage revision surgery. The largest study by Wolff et al. on infected bilateral total knee arthroplasty demonstrated improved outcomes with a simultaneous two-staged revision when compared with irrigation, debridement and prosthetic salvage [6]. Concerns exist about the morbidity of a two-stage revision and the immobility and restricted weight bearing on both extremities during the antibiotic spacer period. A series of 16 bilateral infected arthroplasty patients by Zeller et al. noted good results with single-stage exchange and another center reported two cases of successful treatment of bilateral infected THA with a simultaneous single-stage revision [7,17].

Surgical treatment of bilateral infected arthroplasties should consider factors such as the virulence of the organism, medical comorbidities, patient age and functional status. For bilateral acute hematogenous infection, some authors performed an irrigation, debridement and exchange of modular bearing surfaces followed by targeted antibiotic therapy, but these results were limited to case reports [5,8–13,15,16]. For chronic bilateral periprosthetic infections, these case reports described the same therapeutic management as is commonly favored for unilateral infection: two-stage revision with placement of an antibiotic impregnated cement spacer for a period of at least 6-8 weeks before reimplantation [9,14,15]. An interval of several days occurred between each side undergoing surgery in these series, while others performed simultaneous bilateral revision surgery. The decision whether to perform simultaneous bilateral revision surgery for PJI should also consider the patient's medical comorbidities and functional status. With only small retrospective case series in the literature, we can issue a limited recommendation that revising the components likely results in improved outcomes, however we do not have the data to recommend a single-stage or two-stage revision procedure over the other.

We do, however, feel that performing resection arthroplasty of two joints under the same anesthesia represents immense physiological insult to the patient and all efforts should be made to minimize the operative time and blood loss in these patients if bilateral surgery is contemplated. The use of two expert teams to operate at the same time has been suggested by some investigators.

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5.2. TREATMENT: DEBRIDEMENT AND RETENTION OF IMPLANT

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QUESTION 1: What are the indications and contraindications of using debridement, antibiotics and implant retention (DAIR) with exchange of modular components for the management of periprosthetic joint infection (PJI)?

RECOMMENDATION: The best advantage in performing DAIR of the prosthesis is seen in early postoperative PJI and acute hematogenous PJI, defined as symptoms existing for no longer than four weeks, and if the implant is stable. The KLIC and CRIME80 scores may aid in risk stratification.

LEVEL OF EVIDENCE: Moderate

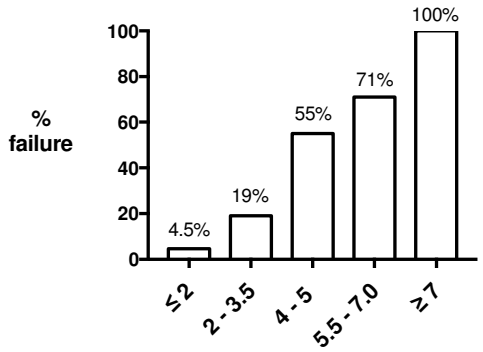
DELEGATE VOTE: Agree: 80%, Disagree: 18%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Open DAIR of the prosthesis is considered a less disruptive intervention that seeks to preserve a functional implant and forego the significant morbidity of implant removal and subsequent surgical procedures. While DAIR remains a viable and a less morbid alternative to resection arthroplasty, recent studies have demonstrated that an unsuccessful procedure is strongly associated with failure of future two-stage revision [1].

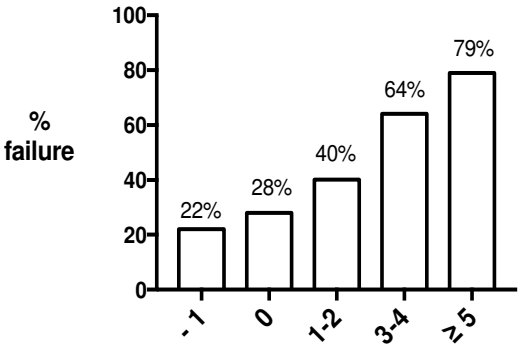
Strictly speaking, there are no absolute contraindications to perform a DAIR procedure, but a DAIR should be discouraged when the chance of failure without removing the implant is very high. Therefore, chronic PJIs should be considered an absolute contraindication to perform a DAIR procedure, as a fully developed mature biofilm with the presence of "persister cells" excludes the possibility for cure without removal of the implant [2,3]. Indeed, Barberan et al. demonstrated in 60 elderly patients with a Staphylococcal infection, that when the duration of symptoms exceeds one month, the failure rate increases exponentially when a conservative treatment is chosen without removal of the implant [4]. Although the efficacy of DAIR in chronic infections have been reported to be around 50% in a recent systematic review with a limited number of 29 patients, the average follow-up of these patients was only one year [5]. Extending the duration of antibiotic treatment following debridement does not seem to increase the chance for cure. Byren et al. clearly demonstrated that prolonging antibiotic treatment for more than six months simply postpones, rather than prevents, failure [6]. For this reason, when the intention is to cure the PJI and the patient is medically fit for major surgery, chronic infections should undergo revision surgery with removal of hardware.

Failure rates following DAIR for acute PJI vary widely and range from 20 - 70%, with higher failure seen in acute hematogenous (late acute) PJI. Contraindications to performing a DAIR procedure in acute PJI are controversial. In general, all acute PJIs are candidates for debridement if the implant is well fixed, but several factors have been associated with an increased chance for failure. These factors include host and implant related factors, the severity and extensiveness of the infection, the duration of symptoms, the possibility to exchange the modular components during debridement and the causative microorganism [1,7–40]. In order to avoid surgery that has a very high risk of failure, selecting a subset of patients that are more likely to benefit from revision surgery instead of DAIR, would be helpful. A preoperative risk score has been developed to predict failure following DAIR for early acute Kidney, Liver, Index surgery, Cemented prosthesis and C-reactive protein value (KLIC-score, Fig. 1A) and acute hematogenous PJIs (CRIME80 score, Fig. 1B) [27,30]. These preoperative scoring systems could be used in clinical practice to select those patients who are most eligible for DAIR.



K	Chronic renal failure (Kidney)	**2**
L	Liver cirrhosis	**1.5**
I	Index surgery: indication prosthesis: fracture OR revision prothesis	**1.5**
C	Cemented prosthesis	**2**
	CRP > 115 mg/L	**2.5**

FIGURE 1A. KLIC preoperative risk score [27,30]



C	COPD	**2**
	CRP > 150 mg/L	**1**
R	Rheumatoid arthritis	**3**
I	Indication prosthesis: fracture	**3**
M	Male	**1**
E	Exchange of mobile components	**-1**
80	Age > 80 years	**2**

FIGURE 1B. CRIME80 preoperative risk score [27,30]

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QUESTION 2: Is debridement, antibiotics and implant retention (DAIR) an emergency procedure for patients with acute periprosthetic joint infection(PJI) or should patient optimization be implemented prior to surgery to enhance the success of this procedure?

RECOMMENDATION: DAIR is not an emergency procedure but should be performed on an urgent basis when the patient with acute PJI is medically and surgically optimized.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 97%, Disagree: 3%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

At the present time DAIR is reserved for patients with acute PJIs when no loosening of the implants is present [1,2]. Success rates vary among different studies from 16% - 82% [3–7]. The large majority of studies regarding DAIR focus on reporting the success rates or evaluating the factors that are correlated with success [2,4–6,8–16]. However, none of these studies have focused on the urgency of DAIR as a procedure.

DAIR should be considered an urgent, but not emergent procedure, as the time period from the onset of symptoms until the operation has been reported to be important factor affecting the success of the procedure [5]. Factors that are known to affect the outcome of DAIR include the type of infecting organism [5,10,17–21], duration of symptoms before intervention [4–7,11–13,17,20,21], type and duration of antibiotic therapy [6,14,22], age [11], erythrocyte sedimentation rate (ESR) values at presentation [4,13,19,20] , presence of underlying inflammatory conditions [4,19], exchange of modular components [7,17,23] and the presence of preoperative comorbidities like anemia [24].

An exact cutoff time beyond which DAIR should not be attempted has not been determined. Nevertheless, the duration of symptoms less than one week has been correlated to a higher success rate [4,5,7,12,17,21]. Furthermore, age of implant ≤ 15 days has been identified as a prognostic factor for successful DAIR [25].

There are patient-related factors and medical comorbidities, which, if not controlled, may result in severe complications and failure of the procedure. Comorbidities, such as rheumatoid arthritis, are not possible to adjust prior to debridement. However, correction of malnutrition, coagulopathy, anemia, hyperglycemia and diabetes should be pursued. Subjecting a patient to irrigation and debridement (I&D) without addressing an underlying coagulopathy could result in the development of a subsequent hematoma and its adverse effects. Thus, it is critical that conditions such as coagulopathy, nutritional status, uncontrolled hyperglycemia (>200 mg/ml), severe anemia (hemoglobin <10 mg/dL) and other reversible conditions are addressed prior to subjecting a patient to DAIR.

In conclusion, we therefore recommend that patients with acute PJI are evaluated on an urgent basis and the surgery is performed when patient is optimized from medical and surgical perspective.

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QUESTION 3: Does identification of the pathogen prior to performing debridement, antibiotics and implant retention (DAIR) help guide the surgeon's decision making? If so, should you wait, in a clinically stable patient, until the pathogen has been identified?

RECOMMENDATION: The identification of the responsible microorganism before DAIR is desirable. However, it should not prevent timely surgical intervention if delay in surgery is believed to promote further establishment of biofilm formation and compromise the outcome of surgical intervention.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

In implant related infections, the need for use of targeted antibiotics with proven action against the infecting pathogen and penetration into the biofilm has been suggested [1]. For instance, experts would likely agree DAIR is appropriate when ciprofloxacin-susceptible *Escherichia coli* is the infecting organism but, would probably discourage DAIR if the infective organism is a *Candida* spp. Thus, from a general perspective, knowledge of the pathogen prior to surgical intervention is desired. However, the real debate is whether waiting to determine the infective organism would adversely affect the outcome of DAIR and the timely intervention. The answer to this question requires an understanding of the implications of delaying DAIR and the consequences of performing DAIR without knowledge of the infecting pathogen.

Regarding the issue of time, Infectious Diseases Society of America (IDSA) guidelines, in conjunction with other authors, recommend a maximum of 21 days of symptom duration before utilizing DAIR to treat periprosthetic joint infection (PJI) [1,2]. This time limit, which has not been identified in comparative studies, is the same as that used in the pivotal clinical trial by Zimmerli et al. on the use of rifampin: none of the patients included in that cohort underwent DAIR beyond 21 days [3]. However, it remains uncertain whether these patients could have benefited from therapy if they had been submitted to DAIR more than 21 days after the beginning of symptoms. To this end, many observational studies have tried to find a precise cut-off of symptom duration, but heterogeneous populations with poorly reproduced results have emerged. Brand et al. observed that as little as a two-day delay in performing DAIR would significantly increase the odds of failure in a cohort of patients with staphylococcal PJI, mainly managed with β-lactams [4]. Other studies have also observed a poor outcome among patients with longer duration of symptoms without identifying a reliable time limit [5–13].

Inability to establish an optimal time threshold for DAIR may be mainly due to two causes. First, a short interval of time for performing DAIR may be a surrogate marker of severity of illness, since patients with sepsis or bacteremia are usually operated on sooner than more stable cases. Ill patients have a higher likelihood of failure [12,14], causing a short duration of symptoms to be paradoxically associated with a worse prognosis.Second, the duration of symptoms may be difficult to establish, especially in post-surgical cases where the postoperative inflammatory signs and pain may overlap the symptoms of infection. In these post-surgical cases, the prosthesis age before DAIR (i.e., the time from prosthesis placement to debridement) may be a more reliable variable. Yet, there is controversy on the definition of an early post-surgical infection that could be managed by DAIR. While IDSA guidelines do not recommend DAIR for patients with PJI that started greater than one month from the index arthroplasty [2], other important studies and the First International Consensus extend this period to three months [1,15]. Two large studies including staphylococcal and streptococcal PJI managed with DAIR found no differences in recurrent infection with a prosthesis age of less than one month versus those that were one to three months old [12,13]. Overall, it seems reasonable to assume that the sooner the DAIR is performed, the better the outcome will be, but there is insufficient evidence to recommend a specific time-limit of symptoms duration beyond which DAIR should be discouraged.

Bearing these considerations in mind, the question falls back onto the influence of the type of infecting microorganism(s) and its antibiotic susceptibility profile on prognosis. Apart from particular and rare situations such as the fungal infection previously mentioned or other multi-drug resistant bacteria, there is limited consensus on the impact of organism type on the outcomes of DAIR. Wide ranges of clinical success rates have been reported for common pathogens when managed by DAIR: 13% - 90% for *Staphylococcus aureus* [4,6,14,16–18], 27% - 94% for gram-negative bacilli (GNB) [8,14,17] and 40% - 94% for streptococci [19–24]. The largest observational studies performed to date set these cure rates in 55% for *S. aureus* [12], 58% for streptococci [13], 51% for enterococci [25] and 68% for GNB (with significant differences between fluoroquinolone-susceptible and -resistant strains: 79% vs.40%. respectively) [26].

Whether a 50% risk of failure should discourage use of DAIR is a matter of controversy. In older patients, Fisman et al. suggested an annual relapse rate ≈ 30% after DAIR to be cost-effective when compared with a two-step exchange procedure [27]. The potential advantages of a successful DAIR (one surgery, bone-stock preservation and less economic costs) [28] should be balanced with the consequences of failure. In this regard, conflicting results have been reported on the consequences of a failed DAIR. Sherrel et al. observed a higher likelihood of relapse among patients undergoing a two-stage revision after a non-successful DAIR, as compared with patients submitted to an elective two-stage exchange procedure [29]. However, these results have been contested by two other observational studies [30,31]. Furthermore, functional outcome has been reported to be identical in patients undergoing two-stage after failed DAIR compared to patients undergoing direct two-stage exchange [30, 31].

In summation, the type of infecting pathogen can be valuable information in the treatment algorithm for patients and surgeons considering DAIR. However, a prompt surgery is also of utmost importance. Therefore, the efforts to identify the causative pathogen for PJI should not cause undue delay in timely surgical intervention. Often, the pathogens of concern are virulent in nature and usually identified soon after culture samples are processed and cultured.

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QUESTION 4: Does exchange of all modular components during debridement, antibiotic and implant retention (DAIR) reduce the rate of surgical site infection (SSI)/periprosthetic joint infection (PJI) recurrence?

RECOMMENDATION: Yes. Exchange of all the modular components during DAIR reduces the risk of PJI recurrence.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 94%, Disagree: 4%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Prosthetic joint infections in the early stage are commonly treated with DAIR. If successful, the outcomes of PJI treated by DAIR show functional outcomes and patient reported outcomes equivalent to those of primary total joint replacements [1]. During this procedure, the removal of modular components allows for better visualization of the knee, especially in the posterior aspect, thereby facilitating proper debridement and potential bio-burden/bio-film elimination. However, it is difficult to judge the necessity of exchanging the modular components during DAIR surgery due to the lack of conclusive evidence.

Our literature review identified several studies that support the exchange of modular components to reduce the rate of PJI recurrence [1–7]. Amongst these, six are retrospective and one is a meta-analysis [7] involving 39 retrospective case-control and cohort studies. Notably, all the studies included in this meta-analysis were also retrospective, making its strength of evidence inherently limited. Furthermore, the success rates after modular exchange during DAIR shows a wide range of variation from 18-83% among different cohorts in various studies. Such wide variations in the impact of modular component exchange suggests that the outcome of DAIR may be associated with multiple factors such as patient selection, thoroughness of debridement, type and virulence of the microorganisms, choice and duration of antibiotic regimen and the definition of treatment failure rather than the exchange of modular components itself. However, a recent systematic review [7] of DAIR performed for total hip arthroplasty showed that the mean proportion of success rate in studies where modular components were exchanged was significantly higher (73.9%) than studies in which no components were exchanged (60.7%). A multicenter review article [5] of 349 patients with *Staphylococcus aureus* PJI of both hip and knee replacements reported that modular exchange reduced the risk of failure by 33%. In addition, PJI review articles [8,9] and Choi et al. [2] study suggest that in total knee arthroplasty, not exchanging the polyethylene was an independent predictor of failure of DAIR (100% failure versus 59% success with modular exchange). Moreover, a recent case-controlled study [3] has shown the ten year implant survival rate of 86% with modular component exchange in DAIR (as compared to 68% without modular exchange) along with a fourfold increase in eradication rate. In contrast, there are several other studies which suggest that modular component exchange is not related to higher success rate of DAIR [8,10–15].

Due to the lack of conclusive evidence in the form of well-designed prospective randomized trials and standardized protocols, only a moderate strength of recommendation is provided for exchanging the modular components during DAIR to reduce the PJI recurrence rate.

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QUESTION 5: What is the minimum necessary volume of irrigation solution to use in debridement, antibiotics and implant retention (DAIR) treatment of acute periprosthetic joint infection (PJI)?

RECOMMENDATION: We recommend that 6-9L of irrigation solution, including saline or antiseptic solution such as sterile dilute povidone-iodine, is used during DAIR treatment of acute PJI.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 90%, Disagree: 7%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

To date, there are no reported clinical studies relating to the optimal volume of irrigation required during DAIR treatment of PJI. However, variable outcomes have been reported with different institutions employing individual protocols for volumes of irrigation.

Few studies provide limited secondary data with regards to the ideal volume of irrigation to be used during total joint arthroplasty (TJA) in general and treatment of an infected joint in particular. In one such study, the authors were able to determine that four liters of sterile saline pulse lavage were sufficient to remove bone and polymethyl methacrylate (PMMA) debris exceeding 1µm in size from the joint during TJA. The authors extrapolated from their results that bacteria might effectively be removed with the same amount of irrigation given the similarity in size to the particulates assessed [1]. This model did not consider the effect of the developing bacterial biofilm on infected arthroplasty implants. DAIR has traditionally been thought to reduce the bacterial load and be effective in the acute period given that bacteria theoretically had not yet formed a glycocalyx biofilm. In another study, the authors used an in vitro model to determine the efficacy of biofilm removal from arthroplasty implants using high-pressure pulsatile lavage. Three liters of normal saline were used over an area measuring 1cm^2 recreating a prosthesis covered in *Staphylococcus aureus* biofilm. The authors concluded that pulse lavage is not able to sufficiently debride pre-existing biofilm. The volume of irrigation solution required was not investigated as a primary endpoint and the authors caution against extrapolating the results to clinical scenarios as their in vitro model potentially overestimated the amount of biofilm debrided by three liters of sterile saline pulse lavage [2]. More important than the volume of irrigation, researchers have found that the presence of staphylococcal infection, an elevated American Society of Anesthesiologists (ASA) score, or purulence were more likely to determine failure.

A comprehensive systematic review of the literature relating to open DAIR treatment of acute postoperative and hematogenous periprosthetic hip and/or knee joint infections, with or without modular component exchange, was performed. Databases searched include: PubMed, Embase, Cochrane Review and Google Scholar. Initial query generated 664 articles. Review articles and book chapters were excluded, while all references from such sources were screened for inclusion (spanning from 1990-2017). We included all Level I-IV studies that specified a certain volume of irrigation used per procedure and recorded the type of solution(s) used, mode of lavage administration, use of additive(s) and number of irrigation and debridements (I&Ds) performed. We included cases whereby some of the modular components may have been exchanged, but excluded those with dedicated planned staged exchanges. A total of 14 studies met the aforementioned criteria (Table 1) [3–16].

Typically, around 6 to 9L of solution were used during a single DAIR treatment, with 12 of the 14 studies utilizing up to 9L or more of irrigation solution. The evidence base for the specific irrigation volume is poorly defined within all studies, and recommendations for specific volumes in both primary and review articles reference consensus data obtained from previously published guidelines or individual protocols. [17–22] Therefore, this systematic review represents the body of evidence of actual irrigation volumes reportedly used in the literature.

No studies currently exist directly linking the necessary volume of irrigation to use in DAIR in acute PJI. Based on several retrospective studies, we extrapolate that the use of 6-9L of irrigation solution may be required when treating acute PJI. Prospective studies evaluating the volume of irrigation used as a study endpoint are required to better elucidate the optimal volume of irrigation in DAIR treatment of PJI.

TABLE 1. DAIR studies

Reference (Author, Year)	Study Design	n (acutePJIs)	Irrigation Solution	Additives	Volume Per Procedure (L)	Modular Revision	Infections Controlled
Mont et al (1997)	Prospective	24	NS	None	10	Yes	83%
Azzam et al (2010)	Retrospective	104	NS	Antibiotics	9	Some	44%
Estes et al (2010)	Retrospective	20	Castile soap solution	None	6 to 9	Yes	90%
Koyonos et al (2011)	Retrospective	102	NS	Antibiotics	9	No	35%
Royo et al (2013)	Retrospective	34	NS	Betadine/Peroxide	9	Some	74%
Kim et al (2014)	Retrospective	20	NS	Betadine	6 to 9	Yes	100%
Moojen et al (2014)	Retrospective	68	NS	None	3 to 6	Yes	21%
Koh et al (2015)	Retrospective	52	NS	None	9	Some	71%
Sousa et al (2016)	Prospective	23	NS	Chlorhexidine	7	Yes	85%
Tornero et al (2016)	Retrospective	143	Sterile Water	None	6 to 9	No	88%
Bryan et al (2017)	Retrospective	90	NS	None	6 to 9	Some	87%
Di Benedetto et al (2017)	Retrospective	20	NS	Betadine	6 to 9	Yes	80%
Duque et al (2017)	Retrospective	67	NS	Betadine/Dakin's/Bacitracin	12	Yes	69%
Narayanan et al (2017)	Retrospective	55	N/A	None	9	Yes	60%

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QUESTION 6: Is there a role for direct intra-articular antibiotic infusion following irrigation and debridement (I&D) for periprosthetic joint infection (PJI)?

RECOMMENDATION: The concept of achieving a minimum biofilm eradication concentration (MBEC) of antibiotics at the site of the infection is compelling. Despite the presence of retrospective studies reporting favorable outcome, because of heterogeneity in terms of adjunctive antibiotics, absence of a control group and small cohort size, the routine administration of intra-articular antibiotics in treatment of PJI is not justified. Prospective, randomized controlled trials (RCTs) are needed to support the routine use of intra-articular antibiotics as a stand-alone or adjunct treatment of PJI.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 92%, Disagree: 6%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Current published evidence for intra-articular antibiotic infusion following irrigation and debridement for PJI is limited to small case series and retrospective cohort studies. The authors of all studies aimed to achieve higher concentrations of antibiotics at the site of the infection than is possible with systemic therapy. PJI is associated with the presence of biofilms and sessile bacteria that are encapsulated within a biofilm matrix are more difficult to eradicate than planktonic bacteria [1–7]. Biofilm is the single most important factor causing resistance of bacteria to antibiotics in the treatment of PJI. While modest antibiotic concentration can prevent biofilm formation, eliminating established biofilm is a different matter. Bacteria protected by biofilm requires concentrations that are orders of magnitude greater than the minimal inhibitory concentration for the planktonic forms of the same bacterium to eliminate resistant organisms that are protected by the glycocalyx.

A systematic review of the literature revealed that biofilm encapsulated bacteria requires MBEC of antibiotics that are several orders of magnitude (100-1000+) above the minimum inhibitory concentrations (MIC) sufficient to eradicate planktonic bacteria (Table 1). Currently, MBECs at the site of the joint infection are not achievable with traditional intravenous (IV) antibiotic therapy without systemic toxicity (Table 1). IV antibiotics generally do not achieve these levels of concentration in synovial fluid, but instead achieve levels around two to three times the MIC.

Even though extensive work has been done to develop adjuvant agents such as antibacterial peptides and chelating agents to reduce the resistance of biofilm bacteria to antibiotics, the only clinically viable method available now is to apply antibiotics directly to the affected joint where the implant resides to achieve concentrations high enough to approach MBEC. The use of antibiotic-impregnated polymethyl methacrylate spacers is the most common method used to deliver antibiotics directly into the joint as part of treatment of PJI. While intra-articular concentration of antibiotics is significantly higher when antibiotic-loaded spacers are used, the level is still an order of magnitude (perhaps thousands of times) lower than what is needed to eradicate the biofilm. Local delivery of antibiotics with antibiotic-laden bone cement does not apply a consistent dose for enough time, with most the elution occurring in the first 48-72 hours and by day 5, the concentrations are often sub-therapeutic [8]. Time is an important factor in management of biofilm and exposure to high concentrations for long periods enhances the ability to achieve MBEC.

Direct antibiotic infusion through an infusion pump can achieve extremely high local levels of antibiotics for a prolonged period.In addition, when the antibiotic is delivered through an external portal, it can be discontinued if toxicity or sensitivity occurs. Perry et al. were the first group to describe intra-articular instillation of antibiotics in 1992 [9]. They used an implantable pump with a catheter from the wound surface, to deliver 200-350 mg of amikacin in a 50mg/ml dilution for 8-15 weeks, to 72 patients with acute infections. Of these patients, 49 underwent debridement and retained their prostheses and 23 had their prostheses removed after the initial debridement. They only reported in detail on a subset of 12 patients (10 knees and 2 hips, median age of 59) with no prior history of infection and with a 37-month follow-up. Local levels of antibiotics were assessed by assaying wound drainage or synovial fluid and ranged from 150 ug/ml to 1688 ug/ml. Serum levels were 10ug/ml, except for one patient whose serum concentration rose to 13ug/ml. Two patients developed recurrent infection, one with the same organism *Staphylococcus aureus (S. aureus)* and the other patient was infected with *Staphylococcus epidermis,* after originally infected with *S. aureus.* In the series of 49 patients who retained their prostheses, 38 patients were infection free, however, follow-up times ranged from 1-58 months.

Fukagawa et al. reported on their experience with 15 patients (16 knees) treated for PJI with stable prostheses [10]. A causative microorganism was identified in eight patients. Patients were treated with open synovectomy, debridement, exchange of polyethylene insert and retained their implant. In the five patients with tumor megaprostheses, the anchors were retained. A Hickman catheter was inserted percutaneously and organism specific antibiotics (if an organism was cultured) were infused into the joint space twice per day until clinical signs of infection resolved, and white blood cell (WBC) count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) normalized, at which point the catheters were pulled. The mean infusion duration was 20.8 days +/- 11.7 days. Intra-articular antibiotics used were: amikacin (400 mg/day), gentamicin (80mg/day) and arbekacin (200 mg/day). No serum antibiotic levels were reported. All patients also received IV or oral antibiotic therapy for 1-3 months. All patients were considered infection free and clinically healed during the first follow-up period of 46.7 months (±25.7 months). However, four of the five knees treated with tumor megaprostheses developed recurrent infection after a mean of 28.3 (±26.1 months). These patients were treated with intra-articular antibiotics again for 13-22 days and the infection was clear at last follow-up. No local toxicity or infection at the catheter site was reported.

Tsumura et al. [11] reported on the treatment of early knee PJI in ten patients with continuous, concentrated, antibiotic irrigation for 7-29 days. Antibiotics were administered through a Salem double lumen catheter after debridement with implant retention. Eight of the 10 patients were infection free and able to retain the original prostheses. The two failures were the only patients with methicillin-resistant *Staphylococcus aureus* (MRSA). Antibiotics administered were: clindamycin, amikacin, cefotiam, imipenem, arbekacin, piperacillin, cefazolin, ampicillin and vancomycin. No serum or synovial antibiotic levels were reported.

In two recent publications, Whiteside et al. reported on a retrospective cohort of 18 total knee arthroplasty (TKA) patients with recurrent knee PJIs treated with single-stage (10 patients) or two-stage revision arthroplasty (8 patients), including 3 patients that required limb lengthening and soft tissue expansion [12,13]. Intra-articular antibiotic infusion using a Hickman catheter was performed as an adjunct to meticulous debridement. The authors administered 100 mg of vancomycin or 20 mg of gentamicin in 3 mL of saline into the joint space and increased the dosage to 500 mg of vancomycin or 80 mg of gentamicin in 8 ml of saline, every 12 or 24 hours as tolerated, once the wound was stable and dry. Patients were also treated postoperatively with 1 gm of IV vancomycin and 80 mg of IV gentamicin for 48 hours. The intra-articular antibiotics were continued for six weeks, with intra-articular vancomycin levels ranging from 10,233- 20,167 mg/L. Mean serum vancomycin peak and trough levels were 4.1+/- 1.2 µg/mL and 3.3 +/- µg/mL respectively. Three patients had to have a reduction in the antibiotic dose due to excessive rise in the level of antibiotics. Follow-up ranged from 2.3-12 years, with a mean of 6.1 years. One patient had a recurrent, postoperative infection at 13 months. No other patients had clinical or serological signs of infection and no patient was placed on chronic suppressive antibiotics. Similarly, Roy et al. compared synovial concentrations of antibiotics with IV vs. intra-articular administration in a subset of patients in the Whiteside study cohort, and found an average, peak intra-articular vancomycin concentration of 9,242 ± 7,608 mg/L following intra-articular antibiotic infusion compared to an average intra-articular concentration of 6.8 µg/mL following IV administration [14]. These data suggest with reasonable certainty that direct intra-articular infusion of antibiotics offers a significant benefit in treating resistant organisms, but certainly do not rise to the same level of evidence as would a RCT performed at the same center.

Revision after reinfected, two-stage revision total joint arthroplasty is an especially challenging clinical problem and is even more difficult when multiple failures have occurred. The complication rate of using antibiotic spacers is substantial including dislocation, fracture and migration of the spacer with bone loss that must be considered when contemplating a second two-stage exchange procedure. A revision with intra-articular antibiotic infusion may play a role in this scenario to reduce morbidity. Antony et al. described intra-articular antibiotic infusion as an adjunct to single-stage revision for previously failed single- or two-stage revision for knee, hip or shoulder PJI, in 57 patients with a mean age of 65 years [15]. Hickman catheters were used for intra-articular infusion of organism specific antibiotics for approximately 4-6 weeks, once or twice per day without concomitant systemic antibiotics. The intra-articular antibiotic dose administered was determined to be 50% of the serum dose given the enclosed space. Infection eradication was defined as negative culture, and normal ESR and CRP and 89.5% of patients were successfully treated at 11 months follow-up. Synovial levels of antibiotics were not collected.

TABLE 1. Therapeutic range, toxicity, minimum biofilm eradication concentration (MBEC), and minimum inhibitory concentration (MIC) of antibiotics used to treat biofilm-encapsulated bacteria

Antibiotic	Therapeutic Range	Toxic Plasma Concentration	*S. aureus*		*MRSA*		*P. aeruginosa*		*S. epidermidis*		*E. coli*	
			MIC	MBEC	MIC	MBEC	MIC	MBEC	MIC	MBEC	MIC	MBEC
Azithromycin	0.04-1	-			512	5120		2560				
Ceftazidime	<150	-					1-4	2560-5120				
Ciprofloxacin	2.5-4	11.5			0.06->32	256 - 1280	0.25-2	80-1280				
Clindamycin	<0.5	-			0.015 - 0.06	64 - >1024						
Colistin	1-4	-										
Daptomycin	6-10	-	0.25	600	0.125	1014						
Doxycycline	<10	30			0.064 - 0.125	64 - 128						
Erythromycin	0.5-6	12-15	1	6400	0.12 - >256	64 - >1024		2560				
Gentamicin	5-10	12	1	6400	0.06 - 64	1 - >256		512xMIC				
Linezolid	0.5-4	-	1	6400	1 - 2	4 - >1024						
Piperacillin	5-20	-					4-128	>5120				
Rifampicin	0.1-10	204	0.16	40								
Tobramycin	5-10	12-15	1	160-4000	1	≥8000	0.2-16	250-2560	32	≥8000	2	62.5-125
Vancomycin	<5-10	30	2	2000-8000	0.25 - 2	2000-8000			2	1000-8000		

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QUESTION 7: Can debridement, antibiotics and implant retention (DAIR) be utilized in patients with an acute chronic infection of a unicompartmental knee arthroplasty (UKA)?

RECOMMENDATION: In the event of acute infection following UKA, early DAIR can be considered. However, if initial treatment effort results in failure or chronic infection is present, the implanted prosthesis should be removed and a one-stage or two-stage conversion to total knee arthroplasty (TKA) should be performed in combination with antibiotic therapy.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 2%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

The main reasons for revision of UKA are loosening, progression of osteoarthritis to another compartment and infection [1]. The incidence of infection after UKA at 0.2 to 1% is lower than that reported after total knee arthroplasty (TKA) [1,2]. A distinctive feature of UKA infection is that both the prostheses and the native cartilage are involved [1]. This is in part attributed to the use of minimally invasive exposures, with less damage to the adjacent soft tissue and sparing of bone and ligamentous structures [3].

In the event of immediate or acute infection following UKA, early irrigation and debridement followed by antibiotic administration can be a proper treatment solution. However, if the initial treatment effort ends up in failure or chronic infection is present, the implanted prosthesis should be removed and a one- or two-stage revision surgery should be carried out [3]. Labruyere et al. reported on failures for nine infected UKA cases managed with one-stage irrigation, debridement and conversion to TKA in combination with three months of antibiotic therapy [1]. Of note, five of these cases first failed DAIR. Kim et al. reported management of five infected UKA cases with two-stage conversion to TKA [3]. Bohm et al. reported two infected UKAs, one of which was managed with one-stage conversion

TABLE 1.Summary of infected UKA cases in the literature

Author/Year	N (infected UKA cases)	Failed DAIR	Treatment	Failures	Follow-up
Labruyere 2015[1]	9	5	one-stage conversion to TKA (9)	0	Median 60 months
Bohm 2000[4]	2 (0.7% infection rate)	?	one-stage (1) two-stage (1)	1 (AKA)	Mean 4 years
Saragaglia 2013[5]	8 (2% of failed UKAs)	?	?	?	?
Kim 2016[3]	5 (0.3% infection rate)	?	two-stage (5)	?	?

successfully and the other was treated with two-stage conversion, ultimately resulting in above the knee amputation [4].

In the setting of UKA, recommendations are weak as only five published papers examine the results of failed UKA, including infection and the rate of infection is very low (Table 1). Two of the infected UKA cases in one study [1] had been post-traumatic infections prior to implantation of the UKA and thus represent more complex scenarios potentially predisposing to treatment failure. There is no literature directly evaluating the role of DAIR in the setting of UKA. However, subsequent failure due to progression of osteoarthritis (OA) occurred in two cases (survival 49%) at an average of three years. Therefore, it may be advisable to proceed with one- or two-stage conversion to TKA at the time of infection in the setting of UKA to minimize the need for additional revision procedures in the future and prevent associated morbidity.

In general, the surgeon should assess prior UKA function, component position and fixation and condition of alternate knee compartments to determine whether retention of implants with DAIR is an appropriate initial treatment in the setting of infection.

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QUESTION 8: Can debridement, antibiotics and implant retention (DAIR) be utilized in the treatment of acute periprosthetic joint infection (PJI) with a megaprosthesis?

RECOMMENDATION: DAIR is a viable treatment option in acute PJI of a megaprosthesis. The effectiveness of DAIR is still unclear due to lack of comparative data among the treatment options and limited evidence to suggest superiority of any one treatment. The treatment decision must be made on a case-by-case basis and account for underlying medical conditions, infection history, organism characteristics and surgical history. DAIR is most appropriate for acute PJI without complicating factors, such as extensive and pervasive infection by a high virulence or resistant organism.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 1%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

Acute PJI of megaprostheses is a terrible complication and a difficult situation for treatment [1]. Infection rates in patients with megaprostheses have been reported to range from 3% to greater than 30% [1–3]. In principle, the treatment of acute PJI with a megaprosthesis is similar to treatment of other acute PJI, except there is significantly more potential space and a greater soft tissue infectious burden requiring more extensive exposure and debridement [4,5]. The surgical options include DAIR [6–8], one-stage revision surgery [4], two-stage revision with an interval cement spacer [9–11], arthrodesis and amputation [5,8]. Unfortunately, there is limited data on the outcome of these different procedures [1,9]. The lack of comparative data is due to the limited indications for a megaprosthesis as well as the clinical heterogeneity of the affected patients [5]. Additionally, treatment details vary greatly, particularly for DAIR. Specific information on the debridement, the type of irrigation solutions, modular component exchange and local and systemic antibiotic use and duration are generally lacking.

Two-stage revision remains the preferred method for treatment of PJI [8–10]. However, two-stage revision significantly increases surgical and perioperative risks and includes a substantial period of reduced mobility between stages, which has heightened interest in alternative surgical options such as DAIR. DAIR is an attractive option as it may prevent the unnecessary removal of implants, which could result in further bone loss and fracture [6,11,12]. DAIR is also the simpler and less costly procedure with a demonstrated shorter length of hospital stay [13]. The overall goal of attempting DAIR should be to select the cohort of patients in whom successful treatment is most likely.

Sujith et al. summarized the absolute and relative contraindication for DAIR [13]: The absolute contraindications are loose prosthesis, poor soft tissue coverage and compromised bone cement mantle. The relative contraindications are the presence of sinus tracts, methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* (MRSA and MSSA) infection, previously revised joints, immunosuppression, rheumatoid arthritis, polymicrobial involvement, bacteremia, C-reactive protein (CRP) >100 mg/L, erythrocyte sedimentation rate (ESR) >60 mm/h, two or more previous debridements and >3 weeks of symptoms.

The decision to perform DAIR can also be based on the classification of the infection. According to Pilge et al.if intraoperative cultures are positive without other signs of infection (Tsukayama Type I), implant retention is attempted and prolonged systemic antibiotic treatment is recommended. Implant retention should also be attempted with stable arthroplasties in type II or III infections (early postoperative infection or acute hematogenous infection). If there are radiological signs of implant loosening, a one- or two-stage revision must be performed [14,15].

During DAIR, thorough debridement is necessary to improve outcome. All infected and nonviable tissue around a well-fixed prosthesis must be removed. Retained components are irrigated and

scrubbed in an effort to remove biofilm [11,13]. Various antibiotic solutions can be used intraoperatively, including dilute betadine and Dakin's solution. Culture-driven systemic antibiotics are also important for successful treatment and co-treatment with rifampin should be utilized in Staphylococcal PJIs [6]. Prolonged or chronic antibiotic suppression may also be necessary. The use of local antibiotics in addition to the administration of systemic antibiotic agents is an area of consideration. Modular components and the exposed metal of megaprostheses can be covered with antibiotic eluting cement, though there is no clinical evidence comparing the efficacy of such methods versus more simple modular exchange.

The most important factors contributing to treatment failure are longer duration of symptoms, a longer time after initial arthroplasty, the need for multiple debridements, the retention of exchangeable components and PJI caused by MRSA [6,11,12]. One- or two-stage revision should be performed if DAIR fails [11,13].

In general, DAIR is a treatment option for acute PJI with a megaprosthesis with varying levels of success in selected and non-complicated patients. The heterogeneity inherent in these cases makes comparisons difficult and there is always some degree of individualization in choice of treatment.

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QUESTION 9: What factors are associated with the successful treatment of acute periprosthetic joint infection (PJI) using debridement, antibiotics and implant retention (DAIR)?

RECOMMENDATION: The following factors have been shown to be associated with treatment success in acute PJIs treated with DAIR:

- Exchanging the modular components during debridement
- Performing a debridement within at least seven days, but preferably as soon as possible, after the onset of symptoms
- Adding rifampin to the antibiotic regimen, particularly when combined with a fluoroquinolone, in cases of susceptible staphylococci
- Treatment with fluoroquinolones in cases of susceptible gram-negative bacilli

The following factors have been shown to be associated with treatment failure in acute PJIs treated with DAIR:

- Host related factors: rheumatoid arthritis, old age, male sex, chronic renal failure, liver cirrhosis and chronic obstructive pulmonary disease
- Prosthesis indication: fracture as indication for the prosthesis, cemented prostheses and revised prostheses
- Clinical presentation representing the severity of the infection: a high C-reactive protein (CRP), a high bacterial inoculum and the presence of bacteremia
- Causative microorganisms: *S. aureus* and Enterococcoci

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 5%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

The success of DAIR depends on multiple host- and implant-related factors, clinical presentation, intraoperative variables, causative microorganism(s) and their antibiotic sensitivities and the antibiotic regimen. It is of note, that the described factors related to treatment outcome in some studies, are not always confirmed by others. Most factors associated with success of DAIR are demonstrated in retrospective studies, entailing a high risk of selection bias, especially for those factors involving certain treatment strategies. Therefore, prospective validation is critical for most of the described variables and differences between cohorts should be taken into consid-

eration in interpreting risk factors. In addition, the success of DAIR depends on the definition of treatment failure and the total duration of follow-up, which also differed amongst the selected studies.

Factors that are consistently shown in the literature to **increase** the chance of treatment success are:

Exchange of Modular Components

The bacterial load detected on polyethylene is higher compared to metal components of prostheses, presumably due to its rough surface that favors the adherence of bacteria [1]. Therefore, exchanging the modular components will reduce the amount of biofilm present on foreign material. Moreover, removing the modular components during DAIR (i.e., femoral head and/or polyethylene component) provides better access to the joint capsule for radical debridement. Tsang et al. reviewed all cohort studies published between 1977 and 2015 on the outcome of DAIR in hip PJI. The success rate of DAIR in studies where all patients underwent modular component exchange was 73.9% (471/637 patients; 95% confidence interval (CI), 70 to 77) compared to 60.7% (245/404 patients; 95% CI, 56 to 65) in patients in whom modular components were retained ($p < 0.0001$) [2]. In addition, Grammatopoulos et al. demonstrated in a cohort of 82 acute hip PJIs a treatment success of 93.3% when modular components were exchanged versus 75.7% when modular component were retained ($p = 0.02$) [3]. Smaller studies confirm the same in acute PJIs of the knee [4,5]. The beneficial effect of modular exchange was also demonstrated as independent predictors of treatment success in large multi-center cohort studies evaluating the outcome of DAIR in hip and knee PJIs caused by methicillin-resistant and methicillin susceptible *S.aureus* ($n = 345$, hazard ratio (HR) 0.65, $p < 0.026$)) [6], streptococci ($n = 462$, HR 0.60, $p < 0.01$) [7] and solely late acute PJIs ($n = 340$, odds ratio (OR) 0.35, $p = 0.02$).

Performing DAIR within at Least Seven Days after the Onset of Symptoms

Several studies demonstrated that the duration of symptoms are significantly shorter in patients who were successfully treated with DAIR compared to patients in whom treatment failed [8–13]. In most studies, the most prominent difference between success and failure is observed using a symptom duration of one week as optimal cut-off [3,10,11,14,15]. Urish et al. demonstrated a treatment success rate of 53.2% in 216 knee PJIs when DAIR was performed within one week after the onset of symptoms. Additional multivariate analysis in this study showed that the chance of failure increased when DAIR was postponed to two weeks after onset of symptoms (HR 1.68), and further increased after four weeks of symptoms (HR 2.34) ($p = 0.002$) [14]. Grammatopoulos et al. demonstrated a treatment success rate of 90.7% in 82 hip PJIs when DAIR was performed within one week after the onset of symptoms versus 75.0% when DAIR was performed after one week ($p = 0.05$) [3]. As the maximum days of symptom duration was not well described in all studies and chronic PJIs are indeed included in some [3,10,12,14], the beneficial effect of debridement within one week may be overestimated in these studies for solely acute PJIs.However, a study performed in 110 patients who had a maximum of 32 days of symptoms indicates the same conclusion [8,9]. These authors demonstrated that for each additional day of postponing DAIR, the odds of implant retention decreased by 15.7% and 7.5% for hip and knee PJI, respectively. In the same study, multivariate analysis showed that performing a DAIR within five days was an independent predictor for treatment success, with an OR of around 0.05 for both hips and knees (95% CI 0.01 to 0.24). These data support the concept that a DAIR should be performed within one week to increase the chance of treatment success, but should preferably be performed as soon as possible.

The Addition of Rifampin in Staphylococci PJI

In the randomized controlled trial performed by Zimmerli et al. in 1998, 24 patients with an infected orthopaedic implant caused by staphylococci and treated with surgical debridement were randomized to antimicrobial treatment with combination ciprofloxacin/rifampin or with ciprofloxacin monotherapy. Adding rifampin to the antibiotic regimen improved treatment success from 58 - 100% ($p = 0.02$)) [16]. Although relatively small in sample size, this study served as the foundation of adding rifampin to the antibiotic regimen in staphylococcal PJI. Thereafter, the benefit of rifampin was primarily demonstrated in observational studies [6,17–19]. In a prospective study including 86 monomicrobial staphylococci knee PJIs treated with open debridement, rifampin-based regimens had a 40% higher treatment success compared to other regimens ($p = 0.01$) [17]. Moreover, the addition of rifampin has shown to be a strong independent predictor for treatment success in multivariate analyses [6,20]. The greatest beneficial effect of rifampin has been shown when combined with a fluoroquinolone, which can be explained by the effectivity of fluoroquinolones against biofilm and by drug-interactions of rifampin with several other antibiotics but not with levofloxacin, the most frequently used fluoroquinolone. In a retrospective study of gram-positive infections treated with DAIR, Tornero et al. demonstrated that rifampin combined with linezolid, co-trimoxazole or clindamycin (which are known to have a drug-interaction with rifampin) was associated with a higher failure rate (27.8%) compared to a combination of rifampicin with levofloxacin, ciprofloxacin or amoxicillin (8.3%) ($p = 0.026$) [19]. The greater benefit of the fluoroquinolone-rifampin combination therapy compared to other antibiotic regimens was also illustrated by Puhto et al. in a study of 113 patients with acute PJI: compared to rifampin-ciprofloxacin, the HR for treatment failure was significantly increased in the rifampin-other antibiotics group (HR 6.0, 95% CI 1.5 to 28.8, $p = 0.014$), and even higher in patients treated without rifampin (HR 14.4, 95% CI 3.1 to 66.9, $p < 0.01$) [20]. In addition, Senneville et al., observed the same in 41 patients with acute *S. aureus* PJI treated with DAIR: treatment success was 93.8% in the fluoroquinolone-rifampin group, 66.7% in the rifampin-other antibiotics group and 57.1% in regimens without rifampin ($p = 0.11$) [21]. Altogether, these data indicate that adding rifampin to the antibiotic regimen, particularly when combined with a fluoroquinolone, is associated with an increased chance of treatment success in acute PJI treated with DAIR.

The Use of Fluoroquinolones in Gram-negative PJI

The protective effect of antibiotic treatment with a fluoroquinolone is demonstrated in two prospective and one retrospective observational study [19,22,23]. In a prospective cohort of 22 patients with early PJI caused by gram-negative organisms, the use of fluoroquinolones was associated with a lower failure rate (7.1%) compared to other antibiotic regimens (37.5%) ($p = 0.04$) [19]. In addition, in a cohort study of 47 cases, treatment with a fluoroquinolone in susceptible gram-negative bacilli was associated with a better outcome ($p = 0.0009$) and was an independent predictor of treatment success (OR, 9.09; 95% CI, 1.96 to 50; p0.005) [23]. Finally, a large retrospective, multicenter study on gram-negative PJI was performed in 16 Spanish hospitals in which DAIR was performed in 72% of the cases (174/242 cases) [22]. The overall success rate of DAIR was 68%, which increased to 79% in gram-negative PJIs treated with ciprofloxacin. In agreement with the previous study, ciprofloxacin treatment exhibited an independent protective effect in the multivariate analysis (HR 0.23; 95% CI, 0.13 to 0.40; $p < 0.001$). In all of these studies, no propensity score matching was performed to correct for possible selection bias. In addition, it should be noted that in most of the performed studies, oral therapy with fluoroquinolones was compared with oral beta-

lactam antibiotics. Questioning the superiority of fluoroquinolones, Grossi et al. demonstrated that treatment with high dose intravenous beta-lactam antibiotics (alone or with the addition of another antimicrobial agent) was not inferior to treatment with fluoroquinolones [24]. Although this study had a relatively small sample size (n = 76) and included both DAIRs and staged revision surgeries, it does provide some evidence for the possibility that alternative intravenous antibiotic regimens and/or combination therapy may be as effective as treatment with fluoroquinolones. More studies are required to confirm this finding.

Factors that are consistently shown in the literature to **decrease** the chance of treatment success are:

Host-related Factors

The importance of host factors in the outcome of patients with a PJI was highlighted by McPherson et al., who described the first grading of the medical and immune status of the host to predict outcome [25]. However, this grading system was not validated in large cohorts of patients who underwent DAIR. For patients managed with DAIR, three large cohort studies in streptococci, staphylococci and late acute PJI identified patients with rheumatoid arthritis (RA) as an important risk factor for failure [6,7]. This high risk for failure in RA patients has been demonstrated in smaller studies as well [10,26,27]. The most pronounced risk was observed for late acute PJIs, demonstrating a failure rate of 74% in patients with RA versus 43% in patients without ($p < 0.001$), and was shown to be an independent predictor for failure in the multivariate analysis, with an OR of 5.1 (95% CI 1.1 – 24.3, $p = 0.04$). Age has been independently associated with worse outcome in a recent large cohort of late acute PJIs, showing that patients older than 80 years old had a significantly higher risk of failure (OR 2.6). In addition, a clear correlation between treatment failure and age has also been described in a large cohort of early PJIs [28]. Male sex [28], chronic renal failure [7,22,29] and liver cirrhosis [29,30] were also identified as independent predictors of failure in patients treated with DAIR. Patients with chronic obstructive pulmonary disease (COPD) showed an increased risk for failure in late acute PJIs only. In this study, COPD was not a significant predictor for failure in the multivariate analysis (OR 2.9, 95% CI 0.99 – 8.68, $p < 0.05$).

Prosthesis Indication

Despite the fact that fracture and revision arthroplasties have a higher predisposition for infection [31–34], these arthroplasties have been associated with a higher risk for treatment failure in acute PJIs as well. Fracture as an indication for the prosthesis has been shown to be associated with DAIR failure in three studies of early acute PJIs [28,29,35] and in one study of late acute PJIs as well. With an average failure rate that is 20 - 30% higher compared to osteoarthritis, fracture as an indication for prosthesis has been shown to be an independent predictor for treatment failure in two studies [29]. The same holds true for revision arthroplasty compared to infected primary arthroplasty, with a failure rate that is 12 - 22% higher [29,36], and even higher in knees [4]. Revision arthroplasty has been shown to be an independent predictor for failure in early acute PJI [29,36]. Only one study demonstrated an increased risk for failure in cemented prostheses, with an OR of 8.7 in the multivariate analysis [29].

Clinical Presentation

Several factors considered as surrogate parameters for the severity of the infection have been associated with treatment failure: a high CRP at clinical presentation [6,23,28,29,37], the amount/percentage of positive intraoperative cultures representing the bacterial inoculum [28,29] and bacteremia/sepsis [7,28,29,38]. In most of these studies, these factors are closely correlated to one another. In case of CRP value, an average cut-off value of > 115 mg/L has been associated with an increased failure rate, depending on the type of infection (late acute or early acute). Notably, late acute/hematogenous infections appear to be associated with worse outcomes compared to early acute/post-surgical infections, especially when the infection is caused by *S. aureus* [6,15,20,37–41].

Causative Microorganism

It has been demonstrated in several studies that an infection caused by *S. aureus* is associated with an increased risk of failure [28,36,42,43]. In a large retrospective cohort of 386 early acute PJIs performed by Löwik et al., the percentage of failure was 17% higher when the infection was caused by *S. aureus* compared to other microorganisms (47.5% vs.30.2%, $p < 0.001$). *S. aureus* infection was also a prominent risk factor for failure in late acute PJIs, illustrated by an OR of 3.52 for *S. aureus* in the multivariate analysis. Methicillin-resistant *S. aureus* (MRSA) infection was associated with an increased risk for failure in a study performed by Cobo et al., but this was not demonstrated as an independent variable in the multivariate analysis [40]. Indeed, Lora-Tamayo et al. clearly demonstrated that MRSA infections have similar failure rates as methicillin-susceptible *S. aureus*, although the time to failure differs [6]. Next to *S. aureus*, overall, poor outcomes have been described for enterococcal PJIs [43–46]. The largest analysis on enterococcal PJI have been performed by Tornero et al., who reported a failure rate of 53% in 94 patients treated with DAIR [45]. Subanalysis demonstrated that infection caused by *E. faecium* have a worse outcome than those caused by *E. faecalis* (72% vs. 42% failure, $p < 0.04$). Indeed, two studies identified the presence of enterococci as an independent risk factor for failure in acute PJI treated with DAIR [43].

Ultimately, a clinical risk score including the most potent factors associated with treatment failure and treatment success should be developed to predict the individual chance of treatment success. One of the main objectives of risk scores would be to identify patients with high failure rate using DAIR. To be of most clinical use, these scores should preferably include preoperative variables only. So far, two articles described a risk score for failure in early acute PJIs (KLIC-score, Fig. 1A) [29] and late acute PJIs (CRIME80-score, Fig. 1B) treated with DAIR. These risk scores can aid in the clinical decision making to choose an alternative surgical approach and/or to intensify the antimicrobial regimen.

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TABLE 1. Literature review of factors associated with successful treatment of acute PJI using debridement, antibiotics, and implant retention

Author, Year	N	PJI	Variables	Failure Rate	Univariate (OR or HR)7	Multivariate (OR or (a)HR)7
Tsang, 2017 [2] Meta-analysis	1296	Early & late	Symptoms≤7 d vs. >7 d Exchange of modular components (yes vs. no)	28% vs. 48%, p = 0.0001 26% vs. 39%, p = 0.0001	-	-
Grammatopoulos, 2017 [3]	82	Early & late	Symptoms≤7 d vs. >7 d Interval since arthroplasty ≤6 w vs. >6 w Exchange of modular components (yes vs. no)	9% vs. 25%, p = 0.05 7.5% vs. 27.5%, p = 0.01 6.6% vs. 24.4%, p = 0.02	-	-
Zhang, 2017 [4]	34	Early & late	Exchange of modular components (yes vs. no)	39% vs. 100%, p = 0.008	-	-
Choi, 2011 [5]	32	Early & late	Exchange of modular components (yes vs. no)	47% vs. 100%, p = 0.001	-	-
Lora-Tamayo, 2013 [6]	345	Early & late	ImmunesuppresionImmunosuppression (yes vs. no) Bacteremia (yes vs. no) Polymicrobial (yes vs. no) CRP Exchange of modular components (yes vs. no) Need of ≥2 debridements (yes vs. no) [2]levofloxacin+rifampin [3]vancomycin+rifampin	71% vs. 43%, p = 0.006 65% vs. 41%, p = 0.001 59% vs. 41%, p = 0.005 NP, p = 0.001 41% vs. 56%, p = 0.004 71% vs. 41%, p = 0.003 NP, p = 0.008 NP, p = 0.02	2.31 2.29 1.76 1.29 0.56 1.98 0.50 0.34	2.23 1.81 1.77 1.22 0.65 1.63 0.42 0.29
Lora-Tamayo, 2017 [7][8]	462	Early & late	[8]Chronic renal failure (yes vs. no) [8]Rheumatoid arthritis (yes vs. no) [8]Immunesuppression (yes vs. no) [8]Revision (yes vs.no) [8]Late post-surgical infection (yes vs. no) [8]Bacteremia (yes vs. no) [8]Exchange of modular components (yes vs. no)	54.5% vs. 40.8%, p = 0.05 64.9% vs. 40.0%, p < 0.01 60.4% vs. 39.9%, p < 0.01 53.6% vs. 38.3%, p < 0.01 62.9% vs. 38.2%, p < 0.01 47.7% vs. 37.9%, p = 0.02 33.0% vs. 51.6% , p < 0.01	1.58 2.23 1.86 1.60 1.41 1.44 0.59	- 2.36 - 1.37 2.20 1.69 0.60
Wouthuyzen-Bakker, 2018 [8]	340	Late	Gender, male vs. female Age, > 80 y vs.≤ 80 y old COPD (yes vs. no) Active malignancy (yes vs. no) RA (yes vs. no) Immunesuppression Immunosuppression (yes vs. no) Fracture (yes vs. no) Revision (yes vs. no) CRP >150 vs. ≤150 mg/L Bacteremia (yes vs. no) S. aureus (yes vs. no) Exchange of modular components (yes vs. no)	49.1% vs. 40.6%,p = 0.11 54.8% vs. 42.3%, p = 0.06 55.9% vs. 43.8%, p = 0.18 51.7% vs. 44.4%, p = 0.04 74.1% vs. 42.5%, p = 0.001 61.5% vs. 42.9%, p = 0.03 70.6% vs. 41.9%, p = 0.02 54.2% vs. 41.7%, p = 0.04 47.9% vs. 41.7%, p = 0.06 56% vs. 39.8%, p = 0.005 53.9% vs. 38.7%, p = 0.005 36.4% vs. 52.4%, p = 0.004		2.02 2.60 2.90 - 5.13 - 5.39 - 2.00 - 3.52 0.35
Urish, 2017 [14]	206	Early & late	Symptoms ≤7 d vs. >7 d S. aureus vs. other	NP, p = 0.004 NP, p = 0.04	1.77 0.63	1.68 0.59
Koh, 2015 [15]	52	Early & late	Early vs. late PJI	18.7% vs. 47.3%, p = 0.04	-	-

TABLE 1. Literature review of factors associated with successful treatment of acute PJI using debridement, antibiotics, and implant retention (*Cont.*)

Author, Year	N	PJI	Variables	Failure Rate	Univariate (OR or HR)7	Multivariate (OR or (a)HR)7
Triantafillopoulos, 2015 [9]	78	NP	Thyroid disease Duration of symptoms MR-staphylococci	68.7%, p = 0.03 p = 0.0001 57%, p = 0.004	-	-
Kuiper, 2013 [10]	91	Early & late	RA (yes vs. no) Symptoms ≤7 d vs. >7 d Early vs. late PJI ESR>60 mm/h CNS vs. others	70% vs. 30%, p = 0.03 26.6% vs. 48.4%, p = 0.02 31% vs. 71.4%, p = 0.04 NP, p = 0.001 69% vs. 28%, p = 0.009	-	1.2-84[1] 1-18[1] 1.1-366[1] 2.2-98[1] 1.8-309[1]
Marculescu, 2006 [11]	99	Early & late	Sinus tract Symptoms >8d	61%, p = 0.002 51%, p = 0.04	2.85 1.79	2.84 1.77
Buller, 2012 [12]	309	Early & late	Symptoms <21 d vs. ≥21 d ESR Previous infection in the same joint (yes vs. no) Resistant-GP vs. others	NP, p = 0.001 p = 0.02 55% vs. 44%, p = 0.009 65% vs. 44%, p = 0.005	-	-
Hsieh, 2009 [13]	154	Early & late	GN vs. GP	73% vs. 53%, p = 0.002	-	-
Tornero, 2016 [16]	143	Early	Suboptimal vs. optimal (rifampin for GP and FQ for GN) antibiotic treatment	31% vs. 8%, p = 0.004	-	4.92
Puhto, 2015 [20]	113	Early & late	Early vs. late PJI Leukocytes > vs. ≤ $10x10^9$/L Ineffective empirical antibiotics vs. effective [4]Rifampin+ciprofloxacin vs. Rifampin+other vs. other	30.8% vs. 54.3%, p = 0.002 50% vs. 24.6%, p < 0.01 60% vs. 33%, p < 0.006 10% vs. 40% vs. 70%, p < 0.01	- R+C vs. R+O: 6 R+C vs. O: 14	- 3.7 3.2 -
Holmberg, 2015 [17]	145	Early & late	Revision (yes vs. no) Rifampin vs. no rifampin	63% vs. 23%, p = 0.02 19% vs. 59%, p = 0.01	-	-
Vilchez, 2011 [38]	65	Early & late	Early vs. late PJI Need of ≥2 debridements	24.5% vs. 58.7%, p = 0.02 NP, p = 0.001		2.57 4.61
El Helou, 2010 [18]	91	Early & late	Rifampin vs. no rifampin	4% vs. 40%, p = 0.03	-	0.11
Zimmerli, 1998 [16][5]	18	Early	Rifampin+ciprofloxacin vs. ciprofloxacin	100% vs. 58%, p = 0.02	-	-
Senneville, 2011 [21]	41	Early & late	Rifampin+FQ vs. other	6% vs. 32%, p = 0.001	-	-
Martínez-Pastor, 2009 [23]	47	Early & late	FQ vs. no FQ for GN PJI CRP > vs. ≤ 15 mg/dL	7% vs. 52%, p = 0.005 50% vs. 17%, p = 0.04	-	9.09 3.57
Tornero, 2015 [29]	222	Early	Chronic renal failure (yes vs. no) Liver cirrhosis (yes vs. no) Femoral neck fracture / revision surgery vs. primary Cemented prosthesis (yes vs. no) CRP > vs. ≤11.5 mg/dL	60% vs. 20%, p < 0.001 48% vs. 21% , p = 0.004 35% / 38% vs. 16%, p = 0.003 25% vs. 19%, p = 0.39 56% vs. 16%, p < 0.001	-	5.92 4.46 4.39 / 4.34 8.71 12.3
Rodriguez-Pardo, 2014 [22]	174	Early & late	Ciprofloxacin (yes vs. no) Chronic renal failure	21% vs. 60%, p < 0.001 NP, p < 0.02	-	0.23 2.56
Grossi, 2016 [24]	35	Early & late	Ciprofloxacin (yes vs. no)	21% vs. 28%, p = 0.65	-	-

TABLE 1. Literature review of factors associated with successful treatment of acute PJI using debridement, antibiotics, and implant retention (*Cont.*)

Author, Year	N	PJI	Variables	Failure Rate	Univariate (OR or HR)7	Multivariate (OR or (a)HR)7
Löwik, 2018 [28]	386	Early	CRP >115 vs. ≤115 mg/L Gender, male vs. female Left-sided prosthesis (yes vs. no) Sepsis (yes vs. no) Ischaemic heart disease (yes vs. no) Fracture (yes vs. no) Gentamicin impregnated beads or sponges (yes vs. no) S. aureus (yes vs. no)	55.2% vs. 30.3%, p < 0.001 46.6% vs. 33.2%, p = 0.08 46.7% vs. 31.1%, p = 0.002 52.1% vs. 35.1%, p = 0.007 50.6% vs. 35.3%, p = 0.013 52.8% vs. 33.3%, p = 0.047 43.0% vs. 23.7%, p = 0.001 50.2% vs. 36.6%, p = 0.022		- 2.03 1.80 - 1.84 - NP NP
Hsieh, 2013 [26]	154	Early & late	RA (yes vs. no)	78% vs. 48%, p = 0.002	-	-
Son,2017 [27]	25	Early & late	RA (yes vs. no)	50% vs. 5%, p = 0.04	-	-
Tornero, 2014 [30]	160	Early	Liver cirrhosis (yes vs. no) CRP > vs. ≤12 mg/dL GN not treated with a FQ vs. treated with a FQ	67% vs. 29%, p < 0.001 47% vs. 29%, p = 0.04 57% vs. 31.5%, p = 0.005	-	12.4 1.06 6.5
Bergkvist, 2016 [35]	35	Early	Hip fracture (yes vs. no)	64% vs. 19%, p = 0.01	-	8.3
Byren, 2009 [36]	112	Early & late	Arthroscopy vs. open S. aureus vs. others Revision vs. primary	53% vs. 12%, p = 0.008 30% vs. 24%, p = 0.05 34.6% vs. 12.8%, p = 0.008	5.4 2.6 2.6	4.2 2.9 3.1
Vilchez, 2011 [37]	53	Early	CRP > vs. ≤ 22 mg/dL Need of 2nd debridement (yes vs. no)	54.5% vs. 16.6%, p = 0.01 75% vs. 18.4%, p = 0.006	-	20.4 9.8
Rodriguez, 2010 [39]	50	Late	S. aureus GN	62.5%, p = 0.01 0%, p = 0.01	3.08 0.46	5.3 0.6
Cobo, 2011 [40]	139	Early	MRSA (yes vs. no)	66.6% vs. 39.6%, p = 0.05	-	None
Tande, 2016 [41]	43	Late		66.6% vs. 39.6%, p = 0.05		
Letouvet, 2016 [42]	60	Early & Late	Number of prior surgeries S. aureus (yes vs. no) Antibiotic treatment < 3 months	p = 0.03 50% vs. 22%, p = 0.02 46% vs. 23.5%, p = 0.01	2.7 3.4	6.3 9.4 20
Soriano, 2006 [43]	47	Early	Enterococcus spp or MRSA vs. others	87.5% vs. 9%, p = 0.003	-	17.6
Kheir, 2017 [44][6]	87	Early & Late	VSE VRE Polymicrobial with enterococci	35% 50% 56%	-	-
Tornero, 2014 [45][6]	203	Early & Late	VSE VRE	41.8% 72%	-	-
Duijf, 2015 [46]	44	Early	Enterococcus sp	34%	-	-

CRP, C-reactive protein; PJI, periprosthetic joint infection; NP, information not provided; MR, methicillin-resistant; ESR, erythrocyte-sedimentation rate; CNS, coagulase-negative staphylococci; GP, gram-positive cocci; GN, gram-negative bacilli; FQ, fluoroquinolone; VSE, vancomycin-susceptible enterococci; VRE, vancomycin-resistant enterococci; RA, rheumatoid arthritis.

[1] Confidence interval 95%.

[2] Sub-group analysis of patients with a post-surgical PJI due to methicillin-susceptible *S. aureus* (MSSA).

[3] Sub-group analysis of patients with a post-surgical PJI due to methicillin-resistant *S. aureus* (MRSA).

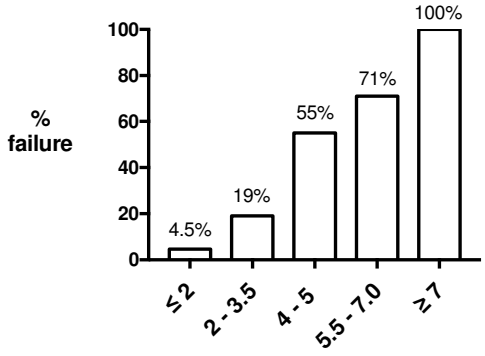
[4] Sub-group analysis of patients with a post-surgical PJI due to staphylococci.

[5] Randomized, placebo-controlled, double-blind trial.

[6] Including patients treated with DAIR and prosthesis exchange.

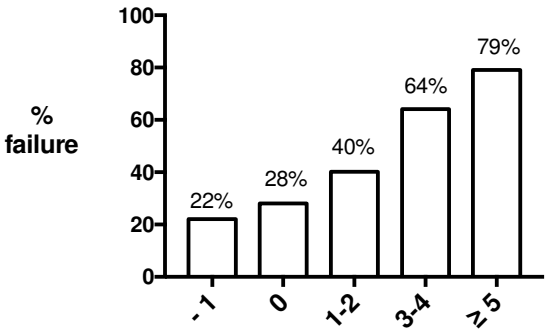
[7] Only depicted when p-value < 0.05.

[8] Only depicting the results associated with overall failure.



K	Chronic renal failure (Kidney)	**2**
L	Liver cirrhosis	**1.5**
I	Index surgery: indication prosthesis: fracture OR revision prothesis	**1.5**
C	Cemented prosthesis	**2**
	CRP > 115 mg/L	**2.5**

FIGURE 1A. KLIC preoperative risk score [19,28]



C	COPD	**2**
	CRP > 150 mg/L	**1**
R	Rheumatoid arthritis	**3**
I	Indication prosthesis: fracture	**3**
M	Male	**1**
E	Exchange of mobile components	**-1**
80	Age > 80 years	**2**

FIGURE 1B. CRIME80 preoperative risk score [19,28]

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QUESTION 10: Does performing a debridement, antibiotics and implant retention (DAIR) affect the outcome of a subsequent two-stage exchange arthroplasty?

RECOMMENDATION: Unknown. Based on the available evidence, it is not known if prior DAIR adversely affects the outcome of a subsequent two-stage exchange arthroplasty.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 6%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

There are several surgical treatment options for periprosthetic joint infection (PJI), including irrigation and debridement (I&D) with modular component exchange and one- or two-stage exchange arthroplasty, with the ultimate choice depending on a number of variables, including chronicity of infection, organism and antibiotic sensitivity patterns, host factors and experience of surgeon. I&D with implant retention has been an attractive strategy in select circumstances as it is less morbid for the patient and less costly to the healthcare system overall. However, the failure rate of I&D is not insignificant, averaging 68% in the literature (61-82%). Following treatment failure of an I&D, the recommendation for subsequent treatment is often a two-stage exchange arthroplasty. The question remains whether the initial attempt at I&D adversely affects the outcome of the subsequent two-stage exchange arthroplasty.

Two earlier studies and one very recent study on this subject seemed to indicate that failure of an initial I&D and modular component exchange leads to a higher than expected failure rates of subsequent two-stage exchange arthroplasty. Sherrell et al. performed a multicenter retrospective review of periprosthetic knee infections treated with a two-stage procedure following an initial treatment

with I&D [1]. Of the 83 knees that had undergone prior I&D, 28 (34%) failed subsequent two-stage revision and required reoperation for persistent infection. With the numbers available, there was no difference between success and failure with respect to age, gender or American Society of Anesthesiologists (ASA) grade. The other earlier study was a retrospective review of 44 patients who had undergone I&D for acute periprosthetic knee infections identified from the HealthEast Joint Replacement Registry and the Minneapolis Veterans Affairs Medical Center (MVAMC) total knee arthroplasty (TKA) database [2]. Of the 25 (57%) patients who failed an attempt at an I&D, 19 went on to an attempted two-stage revision procedure, and in only 11 of these 19 cases (58%) was the two-stage revision procedure ultimately successful. In a very recent retrospective review of 184 PJIs, Rajgopal et al. reported a 23.86% (21/88) failure rate after two-stage exchange following failed I&D compared to 15.62% (15/96) after direct two-stage exchange [3]. The success rate of the subsequent two-stage exchange arthroplasty procedures in all of these series is lower than historical published results, which the authors conclude may be due to the infection becoming more entrenched in the soft tissues and bone.

Two more recent studies on this topic report the opposite findings, namely that I&D before a two-stage exchange does not increase the risk of failure. Brimmo et al. used the California and New York State Inpatient Databases to identify all two-stage exchange revision TKA patients and compared failure rates, as defined as subsequent surgery due to infection within four years, between those with and without prior I&D [4]. Of the 750 patients who underwent two-stage exchange arthroplasty from 2005-2011, 57 (7.6%) had undergone a prior I&D.After four years, the estimated failure rate was 8.7% (95% confidence interval (CI), 1.9%-16.9%) in the group with prior I&D and 17.5% (95%CI, 14.7%-20.4%) in the group without prior I&D. After adjusting for sex, race, insurance, median household income and comorbidities, the hazard ratio for the group with a failed I&D was 0.49 ($p = 0.122$, 95% CI, 0.20-1.20) which the authors indicate revealed a lower risk of failure compared to the group without prior I&D. Nodzo et al. reviewed their single institutional experience of patients who underwent two-stage exchange arthroplasty for PJI of total knee replacements, which included 132 who had not had an I&D and 45 patients who had a prior failed I&D [5]. The success rates between groups were similar at 82.5% and 82.2%, respectively, and the only variable they studied which decreased the odds of reoperation was the use of greater than 2gm of vancomycin in the spacer construct.

As is evident from the current literature, there is no conclusive evidence whether performing a DAIR affects the outcome of a subsequent two-stage exchange arthroplasty. All of the articles included, whether single institution, multicenter or database derived reported on a small number of patients who actually had a two-stage exchange arthroplasty after a failed I&D ($n = 83, 25, 88, 57, 45$) and therefore small differences in accuracy of coding or interpretation of data could potentially sway the results significantly. For those that support the belief that a failed I&D is associated with a decreased success rate for subsequent two-stage exchange arthroplasty, it may not be due to the infection becoming more established in the periarticular tissue, but that it is a patient or organism selection bias/confounding variable, and those individuals that fail an I&D inherently have a higher risk of failing a subsequent two-stage exchange arthroplasty.

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QUESTION 11: How many debridement, antibiotics and implant retention (DAIR) procedure(s) are acceptable in management of patients with acute periprosthetic joint infection (PJI) of a primary arthroplasty before removal of components needs to be performed?

RECOMMENDATION: After one failed DAIR procedure, strong consideration should be given to removal of components.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 13%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

A systematic review of the literature was conducted utilizing the Medline/PubMed (www.ncbi.nlm.nih.gov/pubmed), Embase (www.embase.com), and SCOPUS (www.scopus.com) databases. Studies in which there was a standard protocol for a second surgery other than DAIR (i.e., repeat surgery to remove antibiotic beads or planned multiple irrigation and debridement) were not included in this review.

The majority of the studies reviewed are limited by their retrospective nature, small sample sizes and lack of differentiation between acute postoperative PJI and late-hematogenous PJI. Most researchers viewed failure of DAIR as an indication for a different therapeutic procedure; thus, most studies were limited to a single DAIR. Studies in which multiple DAIRs were performed had given limited insight in their methodology as to why and when a second procedure was performed. Multiple DAIR procedures were only performed in a small portion of the sample size [1,2].

A retrospective review by Triantafyllopoulos et al. attempted to address the appropriate number of DAIR procedures a patient should undergo before resection arthroplasty should be performed. In this retrospective series of 141 patients who underwent DAIR for treatment of a deep periprosthetic infection after primary or revision total knee arthroplasty (TKA) or total hip arthroplasty (THA),

19 patients underwent multiple DAIR procedures [3]. Of the 19 patients who underwent multiple (two or three) DAIR procedures, 10 (52.6%) achieved implant retention with infection control. Of the 122 patients who underwent a single DAIR, 78 (63.9%) achieved implant retention with infection control. All failures underwent prosthesis removal and two-stage reimplantation. The difference in failure rate between those who underwent multiple DAIR and those who underwent a single DAIR was not statistically significant. This study was limited by several factors. The authors included both primary and revision surgeries, as well as a heterogenous mixture of acute postoperative PJI and late-hematogenous PJI. The manuscript also had no clear protocol for which patients underwent repeat DAIR or a different procedure. Furthermore, there was no protocol for patients to undergo additional DAIR or any notation of the timing. Patients who underwent a second DAIR greater than 20 days after the first DAIR had 97.4% lower odds of achieving success compared to patients undergoing the second procedure less than 20 days after the first [3].

A multicenter retrospective analysis by Urish et al. demonstrated 109 out of 216 patients who underwent DAIR after TKA required an additional procedure [4]. Of the 109 failures, 59 underwent repeat DAIR. Ultimately, of the patients who failed initial DAIR, only 28.4% had DAIR as their final procedure; thus, subsequent irrigation and debridement had a failure rate of over 70%.

Another retrospective study compared 64 patients who underwent DAIR (n = 39) versus two-stage revision (n = 25) within three months of primary TKA. Of the 39 patients who underwent DAIR, there were 24 failures (61.5%) and all 24 underwent repeat DAIR [5]. All 24 DAIR procedures failed to control the infection [5]. The DAIR patients underwent on average 3.2 additional surgical procedures (range 1-6) to control the infection whereas the two-stage exchange patients underwent a mean of 2.2 surgical procedures (range 2-4). A further study by Vilchez et al. of 53 THA and TKA patients with PJI treated with DAIR, demonstrated that the need for a secondary DAIR was predictive of failure [6].

The literature demonstrates a second DAIR procedure has, at best, equivalent success as an initial DAIR procedure. In order to avoid additional surgical procedures, resection arthroplasty should be considered after an initial DAIR procedure.

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QUESTION 12: What is the optimal length of antibiotic treatment following debridement, antibiotics and implant retention (DAIR) for acute periprosthetic joint infections (PJIs)?

RECOMMENDATION: The optimal length of antibiotic treatment following DAIR remains relatively unknown as there is considerable heterogeneity regarding the length, dose and administration of treatment. A minimum of six weeks of antibiotic therapy seems to be sufficient in most cases of PJIs managed by DAIR-provided surgical treatment.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 91%, Disagree: 8%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Acute PJIs may be treated by DAIR [1,2]. In this setting, antimicrobial therapy is administered at high doses during the postoperative period. The median success rate for DAIR for management of acute PJI varies from 34.8 - 100% [3–23]. However, none of the published reports directly compare the outcome of DAIR in relation to the length of antibiotic treatment.

In addition, the details of antibiotic treatment such as the route of administration, dose and the duration of therapy, appear to be missing. Two studies, though not providing the route of antimicrobial treatment, stated that patients undergoing DAIR in the cohort received at least six weeks and a median of seven weeks (range, 3 to 39 weeks) of antimicrobial treatment [9,10]. Majority of the studies reporting the outcome of DAIR [3,5,7,13–18] used an antibiotic treatment regimen based up the algorithm proposed by Zimmerli et al. [1]. The latter consists of 7 to 14 days of intravenous antibiotics, followed by 3 to 6 months of oral antibiotics with activity against bacteria in biofilm (e.g., ciprofloxacin, adjunct therapy with rifampin).

Four studies report that intravenous antibiotic was used in their cohort, with or without adjunctive oral antibiotics during the course of treatment for a median duration of six weeks [8,12,19,24]. A single study discloses that the patients received oral antibiotics only after the DAIR procedure, with a duration of six weeks to lifelong treatment [2]. The remaining 11 studies used a combination of intravenous, followed by oral antibiotic therapy. In these studies, the median duration of intravenous antibiotic therapy was 6 weeks and among the seven studies which reported the duration of oral antibiotics, the median was 16 weeks (range 9 weeks to lifelong).

TABLE 1.Comparative studies addressing the length of antimicrobial therapy in the setting of PJI managed by DAIR

Ref	Design	N	Etiology	Antimicrobials	Observations
26	Observational, retrospective, one center	112	Various	6 weeks of β-lactams/ glycopeptides, followed by oral tratment	Length of therapy did not predict the likelihood of failure
35	Observational, retrospective, comparative, non-randomized, one center	60	Various (mostly Staphylococci)	Common use of rifampin and ciprofloxacin	A 6-week treatment was non-inferior than a 12-week treatment
36	Observational, retrospective, comparative, pre-post design, one center	50	Various (mostly Staphylococci)	Common use of rifampin and fluoroquinolones	An 8-week treatment was non-inferior than long standard treatments (3-6 months)
37	Obervational, retrospective, comparative,non-randomized, multicenter	87	Various (mostly Staphylococci)	Rifampin-based combinations	Same outcomes for 6-week and 12-week treatments
38	Multicenter Randomised Clinical Trial	63	Staphylococci	Levofloxacin + Rifampin	ITT analysis: 8-week treatment was non-inferior than 3-6 months. PP analysis : a trend towards non-inferiority was observed.

All studies included hip and knee prostheses. N, number of patients included (referring to those managed by debridement, antibiotics and implant retention); ITT, intention-to-treat; PP, per-protocol.

There appears to be a wide variation in the length of treatment, route of administration and the type of antimicrobial therapy that is selected for patients undergoing DAIR. The heterogeneity in the literature and the clinical practice may arise as a result of the fact that there are no reliable clinical or biological parameters that allows clinicians to assess the response to treatment and hence determine the optimal length of antimicrobial therapy [25]. There is a weak signal in the literature to suggest that after a "critical" period of antimicrobial therapy, no further improvement in outcome is encountered by extending the antimicrobial treatment. In fact, some investigators have stated that the length of antimicrobial therapy does not influence the outcome of treatment of PJI patients by DAIR [26]. To the contrary some investigators believe that prolonged antimicrobial therapy is more likely to lead to masking of the infection and a delay in identifying treatment failure [26,27].

There is little literature regarding the optimal route of administration of antimicrobial therapy. Majority of treating clinicians would recommend that patients undergoing DAIR should receive intravenous antimicrobials, at least initially. One observational non-randomized comparative study, concludes that the only factor associated with failure was the selection of oral antibiotics and not the duration of treatment [4]. The majority of studies that advocate the use of a six- to eight-week course of antibiotic therapy, state that intravenous antibiotics for two weeks followed by four to six weeks of oral antibiotics is optimal [27–34].

There are three observational non-randomized comparative studies showing no differences in success of DAIR when long or short course of antimicrobials were used (Table 1). In a study by Bernard et al., that included a cohort of 60 patients managed by DAIR, the success rate among patients treated for six weeks of antimicrobials was not lower than those treated for 12 weeks [35]. In 2012, Puhto et al. published a pre-post comparison of 50 patients with PJI treated for 8 weeks vs. 72 patients who received either 3 (hips) or 6 (knees) months of treatment, showing similar success rates (63 vs.67% in the intention-to-treat analysis, and 89 vs.87% in the per-protocol analysis) [36]. More recently, Chaussade et al. analyzed 87 episodes of PJI managed by DAIR, with similar success rates when patients were treated for 6 or 12 weeks [37]. All three studies included knee and hip cases, all type of organisms with a predominance of Staphylococci and varying antibiotic regimen.

One randomized multicenter study compared an 8-week course of levofloxacin plus rifampin vs.a long course, three of oral therapy for hip PJI and six months of therapy for knee PJI in the setting of Staphylococcal PJI managed by DAIR [38]. Although the number of patients included was low, the non-inferiority hypothesis of the 8-week course was proven in the intention-to-treat analysis (success rate of 73 vs. 58% for the short course and long course groups, respectively; n = 66), and a trend towards non-inferiority was observed in the per-protocol analysis (cure rate of 92 and 95%; n = 44) [38]. The results of the DATIPO study, an ongoing French multicenter randomized clinical trial comparing 6 weeks vs. 12 weeks of antimicrobial therapy for patients with PJI undergoing surgical management, including DAIR, is eagerly awaited.

While the results of high level studies are awaited and based on the evaluation of the available literature, it appears that six to eight weeks of antimicrobial therapy is the ongoing standard for patients undergoing DAIR. There is less evidence regarding the optimal route of administration, with majority of the studies advocating the initial treatment should include intravenous route. The type of antimicrobials is also based on the organisms isolated with studies proposing that antibiotics targeting biofilm, such as rifampin, should also be part of the treatment algorithm.

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QUESTION 13: What is the most effective combination of antibiotics in the treatment of acute periprosthetic joint infections (PJIs) caused by methicillin-resistant *Staphylococcus aureus* (MRSA) that has undergone surgical management with debridement, antibiotics and implant retention (DAIR)?

RECOMMENDATION: We recommend a combination of a parenteral antibiotic plus oral rifampin for one to six weeks, followed by rifampin and a companion highly bioavailable oral drug for additional three months, depending on the susceptibility profile of MRSA, patient tolerability and side effect profile.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 88%, Disagree: 10%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Treatment of MRSA PJI that has undergone DAIR remains challenging. An ideal combination of antimicrobial therapy has not been established. Treatment should take into account antimicrobial susceptibilities of MRSA and tailored accordingly. Whenever possible, rifampin-based combinations should be used, but rifampin alone should never be used due to the rapid development of resistance. Rifampin-based combination therapy regimens have been shown to be effective in eradication of staphylococcal organisms and cure PJIs. A widely used algorithm by Zimmerli and the Infectious Diseases Society of America (IDSA) guidelines recommend a quinolone–rifampin combination for susceptible *Staphylococcus aureus* strains and cure rates of 70 - 100% have been reported [1–3]. The duration of antimicrobial therapy for PJI managed with DAIR has not been well established. We recommend two to six weeks of parenteral antimicrobial therapy in combination with rifampin 300 to 450 mg orally twice a day, followed by rifampin plus a susceptible companion oral drug (such as trimethoprim-sulfamethoxazole, ciprofloxacin or levofloxacin, a tetracycline, fusidic acid) depending on the individual tolerance, side effect profile and antimicrobial susceptibility testing [1,4,5]. Certain highly bioavailable drugs such as fluoroquinolones, rifampin, linezolid and trimethoprim-sulfamethoxazole, reach levels in bone that exceed the minimal inhibitory concentration (MICs) for most organisms [6].

Zimmerli et al. have suggested a duration of therapy of three months for total hip arthroplasties (THAs) PJIs and six months for total knee arthroplasties (TKAs) PJIs [1,3]. Shorter courses of therapy (6 vs. 12 weeks) were studied in PJIs treated with DAIR. However, in this study by Chaussade et al. the presence of MRSA, which comprised only 13.8% of infections, was associated with a poorer outcome (remission in 41.7 vs. 73.3% for other pathogens [7]. Chronic oral suppression with trimethoprim-sulfamethoxazole, minocycline or doxycycline based on in vitro-susceptibilities and individual side effect profile and tolerance may be considered following the above regimens and should be reserved for patients who are unsuitable or refuse further surgical therapy. The duration of chronic oral suppression remains unknown.

While the current IDSA guidelines recommend vancomycin as the primary parenteral agent for treatment of MRSA infections, its utility has been questioned due to increasing reports of heterogeneous resistance, treatment failure, and nephrotoxicity. Vancomycin is not bactericidal against small colony variants (SCV) of MRSA. Moreover, Lenhard et al. showed recently in mixed-population experiments that vancomycin favorably selects for the growth of the SCV subpopulation [6]. Therefore, clinicians should consider glycopeptide combination regimens or alternative antimicrobials in patients with severe persistent MRSA infections in which the SCV phenotype may play a role.

In vitro analyses have identified fluoroquinolones and oritavancin as retaining high levels of vancomycin in vitro against SCVs and β-lactam combinations with daptomycin may offer a new option for combating SCVs [8,9,10]. While optimal treatment for infections caused by staphylococcal SCVs is not known, combination therapy including either rifampin or oritavancin appears to be particularly effective at eradicating intracellular SCVs [11].

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QUESTION 14: What antibiotic therapy (agent, route, dose and duration) is recommended for gram-negative acute periprosthetic joint infections (PJIs) being treated with debridement, antibiotics and implant retention (DAIR)?

RECOMMENDATION: Following surgical intervention (DAIR), gram-negative acute PJI patients should also receive antibiotic treatment for 6 to 12 weeks based on the type of organism. In fluoroquinolone-susceptible cases, the recommended antibiotic agent is a fluoroquinolone.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 83%, Disagree: 11%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

In recent decades, the number of PJIs caused by gram-negative organisms, including multidrug-resistant gram-negatives (GNs), has increased [1]. Several studies have been published on antibiotic treatment of these infections in patients treated with surgical debridement and implant retention (DAIR) [2–8]. Studies have been performed demonstrating the preferred antibiotic agent for treating these infections, but few relate to the preferred route, dose and duration of antibiotic treatment.

Antibiotic Agent for GN PJIs Treated with DAIR

Rodriguez-Pardo et al. performed a retrospective analysis on 242 GN PJIs, including 174 cases (72%) treated with DAIR [2]. The study demonstrated that the use of fluoroquinolones (in this study ciprofloxacin) was associated with the highest success rate of 79% (98 of 124), while the success in the remainder of the patients treated with other antibiotic regimen (e.g., β-lactam or cotrimoxazole) was only 40% (20 of 49). In addition, ciprofloxacin treatment exhibited an independent protective effect in the prevention of subsequent failure in the multivariate analysis (adjusted hazard ratio (aHR) 0.23; $p < 0.001$). In addition to endorsing the use of fluoroquinolones, the latter study also favored the use of combination therapy, as a β-lactam antibiotic combined with a fluoroquinolone or an aminoglycoside as this regiment showed a trend towards better outcome (aHR 0.42, $p < 0.07$). The cohort of patients included in the study were mostly infected with *Enterobacteriaceae* spp. (78%) and some with *Pseudomonas* spp. (20%). The study was not able to glean which of the PJI cases benefited from the combination therapy. Several other smaller studies have been performed, supporting the beneficial effect of fluoroquinolones. Aboltins et al. [3] studied the outcome of 17 consecutive patients with an early GN PJI, mostly polymicrobial in origin (76%), and mainly involving *Enterobacteriaceae* spp (94%). All of these patients were initially treated with β-lactam antibiotics intravenously, and 14 patients were subsequently treated with oral ciprofloxacin. Treatment failure occurred in two patients not treated with ciprofloxacin (median period of follow-up of 28 months). Only one of these failures was caused by a relapse with the same GN, suggesting a cure rate of 100% (14/14) when using ciprofloxacin versus 66% (2/3) when using another oral antibiotic regimen (in these particular cases amoxicillin/clavulanic acid). In addition, a study performed by Jaén et al. (n = 47) and Tornero et al. (n = 21) on GN PJIs treated with DAIR, which were partly based on the same cohort of patients, also demonstrated that the use of fluoroquinolones in susceptible GN was the only factor associated with treatment success in the univariate analysis [4,7,8].

Recently, Grossi et al. [9] demonstrated in 76 GN PJIs that the outcome of treatment with IV β-lactam antibiotics (alone or in combination with another antimicrobial agent) during the whole treatment period (median three months) was similar compared to the use of an oral fluoroquinolone (failure rate 16.7 vs. 22.4%, $p = 0.75$). Although the study of Grossi et al. included both DAIRs and revisions as surgical strategy, outcome remained the same after stratification according to the surgical procedure, suggesting that intravenously antibiotic regimens and/or combination therapy may be as effective as treatment with fluoroquinolones.

The use of alternative oral regimens other than β-lactam, like cotrimoxazole, have been poorly studied in the field of PJI and require further investigation.

Only a few data are available on how to treat multidrug-resistant (MDR) GN in the field of PJIs, but extensive reviews and expert opinions have been published, utilizing the efficacy of carbapenems, combined with tigecycline, colistin or fosfomycin when the microorganism is susceptible [10–13]. Another question in the consensus document elaborates on the efficacy of tigecycline and fosfomycin alone or in conjunction with β-lactam in the treatment of PJI, suggesting that tigecycline or fosfomycin could be considered for the treatment of MDR GN PJI of as a part of a combination regimen when the microorganism is susceptible.In addition, the benefit of adding colistin to a β-lactam for osteoarticular infections caused by MDR, have been reported as well, demonstrating a higher cure rate for combination therapy [14,15].

Treatment Suration, Route and Dosage for GN PJIs Treated with DAIR

Table 1 shows the treatment duration and subsequent failure rate of the above-mentioned studies. Whether a short or long treatment duration was associated with a respectively lower or higher cure rate was not described in most studies. Only Jaén et al. evaluated the difference in outcome between patients treated with more or less

TABLE 1. Overview treatment duration and outcome in GN PJIs solely treated with DAIR

Author, Year	Patients (n)	IV (days)	Oral (days)	Total (days)	Failure %
Tornero et al. 2016 [4]	21	8 (IQR 5-12)#	69 (IQR 45-95)#	ND	14
Grossi et al. 2016 [9]	35	36 (IQR 14-90)*	ND	90 (IQR 89-92)*	23
Jaén et al. 2012 [8]	47	14 (IQR 8-24)	64 (IQR 28-102)	ND	26
Rodriguez-Pardo et al. 2011 [2]	174	14 (IQR 6-23)	58 (IQR 27-90).	ND	32
Zmistowski et al. 2011 [5]	10	ND	ND	ND	30
Aboltins et al. 2011 [3]	17	40 (range, 9 - 79)	365 (range, 30 - 1678).	ND	6
Hsieh et al. 2009 [6]	27	38 (range, 24-52)	49 (range, 28-92)	ND	27

*, duration of treatment included cases treated with revision surgery; #, duration of treatment included gram-positive PJIs; IQR, interquartile range; ND, no data.

than 14 days of IV treatment and treated with more or less than 64 days of oral antibiotic treatment and demonstrated no differences in outcome [8]. Although studies have demonstrated an equal success rate with 6 to 8 weeks compared to the standard 12 weeks of antibiotic treatment [16–20], these studies have been mainly performed in rifampin susceptible staphylococci and cannot be extrapolated to GN PJIs. For this reason, we would still recommend a 6 to 12-week treatment duration (including 1 to 2 weeks of IV treatment), especially in ciprofloxacin-resistant GN. In caseβ –lactam is indicated, it should be administered intravenously throughout the entire treatment period.

No studies evaluated the dosage of antibiotic treatment and its relation to outcome. We propose the recommendations depicted in Table 2.

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TABLE 2. Proposed antibiotic regimen for GN PJIs treated with DAIR

Microorganisms1	IV Regimen	Oral Regimen
Enterobacteriacae, ciprofloxacin susceptible	Ceftriaxon 2 gm QD ± Ciprofloxacin 400 mg TID	Ciprofloxacin 750 mg BID
Pseudomonas spp, ciprofloxacin susceptible	Cefepime 2 gm TID *or* Meropenem 2gm TID *or* Ceftazidime 2gm TID *or* Piperacillin-tazobactam 4.5gr QID ± Ciprofloxacin 400 mg TID *or* Tobramycin 7mg/kg QD	Ciprofloxacine 750 mg BID
Enterobacteriaceae, ciprofloxacin-resistant	Ceftriaxone 2 gm QD ± Tobramycin 7mg/kg QD	IV β-lactam antibiotics during the whole treatment period *Possible alternative* Cotrimoxazole 960 mg TID
Pseudomonas spp, ciprofloxacin resistant	Cefepime 2 gm TID *or* Meropenem 2gm TID *or* Ceftazidime 2gm TID *or* Piperacillin-tazobactam 4.5gr QID ± Tobramycin 7mg/kg QD *or* Colistin 3 million IU TID *or* Fosfomycin 2-4g QID	IV antibiotics during the whole treatment period

DAIR, debridement, antibiotics and implant retention; PJIs, periprosthetic joint infections; QD, four times daily; TID, three times daily; BID, twice daily

± Duotherapy can be considered in patients who have a high risk for treatment failure.

1 In case of multidrug-resistant or extremely drug-resistant gram-negative, the antibiotic treatment should be guided by the antibiogram and preferentially by combining two antibiotics with a different mechanism of action.

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5.3. TREATMENT: ONE-STAGE EXCHANGE

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QUESTION 1: What are the potential advantages of a one-stage exchange arthroplasty?

RECOMMENDATION: The potential advantages of a one-stage exchange arthroplasty are multiple, including a decrease in surgical morbidity and mortality, earlier functional return, decrease in healthcare and global economic costs as well as an increase in health-related quality adjusted life years.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 89%, Disagree: 8%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

While multiple studies have been performed evaluating the efficacy of a one-stage or two-stage exchange arthroplasty for periprosthetic joint infection (PJI) [1–13], the majority demonstrated a reduced rate of recurrent infection after a two-stage exchange in comparison to a one-stage exchange, although the comparative value of these results is difficult to interpret given discrepancies in patient comorbidities, bacterial profiles, treatment protocols as well as variances in the definitions of PJIs, clinical success, and failure.

In North America, treatment of PJIs using a two-stage revision procedure remains the most widely utilized and reported method in the literature [14–16]. However, there is no clear evidence that shows superiority of two-stage over one-stage revision in terms of success, eradication of infection or patient satisfaction [1–11,13,16–18]. In addition, one-stage revision has demonstrated multiple advantages in several prognostic and observational studies, particularly within the European literature [1–13].

Depending on the study and follow-up time, one-stage revision procedures have demonstrated a success rate ranging between 75 to 95% [1–5,7–13,17–19]. This is comparable to the reported reinfection rates after two-stage revisions between 9 and 20% of cases [20]. Furthermore, when appropriately performed, one-stage revision can avoid the morbidity associated with multiple surgeries while providing the advantages of reduced total length of stay, overall cost and earlier functional rehabilitation [19,20]. Other advantages include the reduced duration of postoperative systemic antibiotic therapy and systemic antibiotic side effects [19,20].

Despite this demonstrated success of one-stage revisions, it is critical to recognize that this procedure is contingent on strict patient selection criteria and specific operative planning protocols. For example, preoperative identification of the responsible bacterial organism in the synovial fluid is a prerequisite to determine the specific local and systemic antibiotic therapy regimen [3,6,10,11,19]. Also, patients who fail prior one-stage revision, those with an unclear causative pathogen or lack of susceptibility to available antibiotics and those with more extensive infections, may not be candidates for one-stage exchange [20].

In addition to strict selection criteria, several meticulous intraoperative steps, including aggressive soft tissue debridement, meticulous removal of the prior cement material and all hardware, as well as the use of antibiotic-loaded cement for reimplantation, along with specific postoperative antibiotic regimens, are important for success [19]. In a systematic review comparing one- to two-stage exchange, superior outcomes for one-stage revision were reported when performed in this selective patient population [21].

Two recent meta-analyses comparing outcomes for one-stage versus two-stage exchange for patients who have PJIs after both total hip [22] and total knee [23] arthroplasties demonstrated statistically equivalent reinfection rates for both protocols. These findings, were, however limited by the quality of the studies included in the meta-analyses, as well as a relative paucity of studies evaluating one-stage protocols in comparison to two-stage exchange.

Wolf el al. utilized Markov modeling in a decision-tree analysis to suggest a possible superiority of treatment of a one-stage exchange in comparison to a two-stage protocol as it pertains to health-related quality of life years, despite an objective decrease in recurrent infection with a two-stage protocol [24]. Although

the mortality increase in a two-stage protocol was most directly responsible for the predicted advantage of a one-stage protocol in this study, failure of reimplantation in some circumstances, time between procedures and a longer total recovery, were also utility values which favored direct exchange. Although the challenges in conducting an adequately powered randomized controlled trial to properly address this question are multiple, important controversy regarding this topic will likely remain until this is done.

Based on the current evidence, one-stage revision procedures can be utilized as an alternative to two-stage revision for PJIs, with comparable success. However, this may not be a suitable option for all patients with an infected prosthesis. Meticulous operative planning and surgical technique is important to achieve excellent outcomes. Future prospective, randomized, adequately powered, and preferably multicenter studies are necessary to delineate the superiority of a one- or two-stage revision approach for PJIs. It is likely that marked controversy regarding this topic will likely remain until such evidence becomes available.

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QUESTION 2: What are the indications and contraindications for a one-stage exchange arthroplasty for the treatment of chronic periprosthetic joint infections (PJIs)?

RECOMMENDATION: One-stage exchange arthroplasty remains a viable option for the management of chronic PJIs. In patients with signs of systemic sepsis, extensive comorbidities, infection with resistant organisms, culture-negative infections and poor soft tissue coverage, one-stage exchange arthroplasty may not be a good option.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 5%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

The evidence for best practice in the management of PJIs is an evolving science with increasing popularity for one-stage revision arthroplasty over recent years. This popularity is mainly driven by a number of studies reporting comparable [1,2], if not better [3] outcomes of one-stage vs.two-stage exchange surgery and the potential for reduced patient morbidity, mortality and socio-economic burden with the former [4–6]. Excellent outcomes for infection-free survival are documented in the literature, especially where strict criteria for patient selection is met. Haddad et al. [3] in 2015 reported their series of 28 highly selected patients undergoing one-stage exchange for chronically infected knee arthroplasties with a 0% re-infection rate at a minimum of three years follow-up. Their cohort

accurately matched the host, local and microbiological criteria proposed in this updated consensus document. Earlier results from Oussedik et al. in 2010 reported a similar success rate of infection-free survival of one-stage exchange arthroplasty of hip patients in the presence of a strict patient selection protocol [7].

Despite these aforementioned studies, there still remains a lack of high-quality literature addressing the subject matter. Hence, in the absence of published randomized controlled trials, many of our conclusions have been drawn from a combination of retrospective and prospective cohort studies and systematic reviews of these.

Early experience of one-stage exchange arthroplasty by Buchholz et al. [8] in 1981 reported an overall success rate of 77% in a large series of 583 patients. In this study, the microbiological profile appeared to play an important role onthe outcomes, with polymicrobial infections and atypical and gram-negative organisms being associated with a higher failure rate. These findings have later been echoed by Jackson et al. [9] in their literature review in 2000, where they concluded that in addition to these factors, infection with methicillin-resistant *Staphylococcus aureus* (MRSA)/methicillin-resistant *Staphylococcus epidermidis* (MRSE) resistant organisms were associated with poor outcomes. It is important to note, however, that despite these reports, evidence from the HELIOS ENDO-Klinik, where a high volume of one-stage procedures are performed (85% of all septic revision), does not consider these factors as absolute contraindications to one-stage surgery and still has presented promising long-term follow-up [10].

Excellent results have also been reported in a number of series, with 92 - 100% infection free survival, where known microbiological susceptibility had been established preoperatively [3,10–12]. Despite this, the importance of predetermined microbiology has also been indirectly questioned by one or more studies recently [13–15]. Buchholz et al. noted best results in negative culture cases, a criterion previously considered an absolute contraindication for the one-stage strategy. Lange et al., in their series of 56 patients report a 91% infection-free period, despite 15 patients having negative tissue cultures. Furthermore, in their series, only one of the five failures had documented negative culture [13]. Hence, it may be proposed that a lack of preoperative microbiological diagnosis may be considered a relative, rather than absolute, contraindication for one-stage exchange arthroplasty.

Host and local factors have also been highlighted as important determinants of outcome of one-stage revision. A study by Goksan et al. in 1992, on a small cohort of 18 cases, reported a 94% success rate with knees, success defined as eradication of infection. Host profile in this series matched some of the indications criteria later set out by the International Consensus Group in 2013 to include the absence of systemic sepsis and gross tissue inflammation. Of the two reported cases of failure, both patients were noted to have severe immunosuppression [16]. In a retrospective study by Wolf et al. [17], their patient cohort was classified using the McPherson classification system based upon host status and local status. Their series concluded better outcomes in terms of infection eradication with two-stage vs. one-stage procedures being performed in the presence of host systemic compromise (95 vs. 33% eradication for McPherson type B + C patients) and local soft tissue and bony compromising factors (95 vs. 0% eradication for McPherson stage 3 patients). More recently, Bori et al. published their series of 19 consecutive one-stage revision hip cases and reported a 95% cure rate. They noted an absence of important bone defects intraoperatively (with only four cases requiring bone grafting) as a potential contributing factor to their successful outcomes [15].

The presence of soft tissue defects and sinus tracts also appear to have a negative impact on outcomes in some studies with a 27% reinfection rate (6 out of 22 cases) [18]. Similarly, of the five recurrent infections in the series by Lang et al., three patients had soft tissue lesions in the form of a sinus tract at initial presentation and one had an abscess. It is important to note, however, that despite these reported findings, Jenny et al., in an earlier series of 47 patients documented an 87% infection-free survival period at 3 years despite a large number of their cohort of patients (43%) presenting with a fistula. In their series, only two patients with a sinus tract subsequently fell into their reinfection group [19]. Hence, it may be proposed that a discharging fistula is, in itself, not an absolute contraindication to one-stage exchange arthroplasty, a conclusion also drawn by Raut et al. [20].

It may be concluded that one-stage exchange arthroplasty remains a plausible option for the management of chronic prosthetic joint infections in a selected group of individuals with the prospect of promising results for infection-free survival of the revised prosthesis. Much of this evidence, however, is based upon analysis of prospective and retrospective observational studies. Furthermore, the fact that outcomes following one-stage exchange are affected by multiple factors, it is often difficult to assess the impact an individual criterion has. There is no doubt that stronger conclusions may be drawn in the future following results from established randomized controlled trials that are underway in the United Kingdom, United States, and elsewhere. In the meantime, we offer the following as indications and relative contraindications for one-stage exchange arthroplasty.

Indications for One-stage

Host/Local

- Non-immunocompromised host
- Absence of systemic sepsis
- Minimal bone loss/soft tissue defect allowing primary wound closure
- Microbiology
- Isolation of pathogenic organism preoperatively
- Known sensitivities to bactericidal treatment

Relative Contraindication to One-stage

- Severe damage of soft tissues where the direct closure of the joint and the wound is not possible. A complex sinus tract which cannot be excised along with the old scar.
- Culture-negative PJI, where the causative organism and its susceptibility are not known.
- No radical debridement of infected soft tissues or bone is possible (for whatever reason).
- No local antimicrobial treatment is possible (for whatever reason).
- No proper bone stock exists for the fixation of the new implant.

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QUESTION 3: Is there a role for single-stage exchange arthroplasty in acute periprosthetic joint infections (PJIs) of cementless total hip arthroplasties (THAs)?

RECOMMENDATION: Yes. Single-stage exchange arthroplasty can be employed to treat patients with acute PJIs of cementless THAs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 89%, Disagree: 7%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Debridement and retention of implants, single-stage revision and two-stage revision are all described treatment options in the management of PJIs [1]. Since the 1970s, when Buchholz introduced the concept of single-stage revision arthroplasty as an alternative to two-stage revision for PJIs, multiple authors have published similar encouraging results on single-stage revision for infected THA [2–4]. With shorter total hospital stays, less risk of perioperative complications and lower overall healthcare costs, single-stage revision has been considered an attractive treatment option for the devastating complication of hip PJIs [5].

Single-stage exchange arthroplasty for acute PJIs in cementless THAs is a unique situation with pros and cons. On the one hand, the acetabular and femoral components may not have had time to fully osseointegrate. This not only facilitates extraction of implants without incurring significant bone loss, but also allows for the use of "primary type" components for the reimplantation portion of the procedure [6]. On the other hand, one of the primary tenets and keys to the success of Bucholz's original one-stage exchange arthroplasty was the preoperative identification of the infecting organism to help guide the choice of microbe-directed antibiotic cement during the reimplantation of components. In the case of standard "cementless" revision arthroplasty, this is not feasible. As a result, more recently, some surgeons have employed adjunct techniques to achieve similar supra-therapeutic concentrations of antibiotics into the periarticular space during a cementless single-stage revision hip arthroplasty [7,8].

The literature on the topic of one-stage exchange arthroplasty is quite heterogenous, specifically in regards to inclusion criteria, infecting organisms, surgical technique and length of follow-up. Therefore, reaching a definitive conclusion for the role of one-stage exchange arthroplasty in the treatment of acute PJIs of cementless THAs is challenged by the limited available data [6–10]. We identified three clinical studies which reviewed their results of cementless one-stage exchange arthroplasty for acute PJIs of THAs. In a multicenter, retrospective series of 27 patients, Hansen et al. demonstrated a 70% success rate of component retention at a minimum follow-up of 27 months and a mean follow-up of 50 months. However, 4 of the 19 patients required further operative debridement to obtain control of the infection, indicating that an isolated one-stage exchange arthroplasty was successful in only 15 of the 27 patients (56%) [6]. In a study by Wolf et al., which included 24 acute THA infections treated with one-stage cementless exchange arthroplasty, eradication of the infection was achieved in 75% (18/24) at two years mean follow-up [9]. Unfortunately, the study with the longest mean follow-up of 8.6 years only included 6 patients who had undergone one-stage cementless exchange. While they reported no cases of reinfection, they had very strict inclusion criteria for deciding on the one-stage exchange (e.g., negligible pus, healthy patients, no evidence of acute systemic infection) and their infecting organism profile only included *Staphylococcus epidermidis* and one case of *Clostridium,* so the applicability of their results must be interpreted in this light. Similarly, the one study that investigated cementless one-stage exchange arthroplasty for chronic PJIs of THAs by Yoo et al. reported component retention in 10 of 12 patients (83%) at a mean follow-up of 7.2 years, but excluded all patients with PJIs caused by methicillin-resistant *Staphylococcus* aureus (MRSA) [11].

As mentioned earlier, one of the keys to the historical success of the one-stage exchange arthroplasty was the ability to deliver supra-therapeutic concentrations of antibiotics into the periarticular space, which is not feasible in standard cementless two-stage revision arthroplasty. Two authors have developed novel techniques to provide adjunct antimicrobials locally in the hopes of improving their infection-free survival.

Using antibiotic-impregnated allograft bone during single-stage revision for PJI, Winkler et al. showed no recurrence of infection in 34 of 37 (92%) of their patients at a mean follow-up of 4.4 years. They calculated supra-therapeutic concentrations of vancomycin in the drainage fluid up to three days postoperative without systemic adverse renal effects and demonstrated that the antibiotic-impregnated grafts had similar incorporation as the normal allografts [7]. Whiteside and Roy introduced a new concept of antibiotic infusion within the periarticular space after single-stage revision for PJIs using Hickman lines, and by this means they have achieved no reinfections and complete clinical eradications of infection in their 21 cases at five years mean follow-up [8].

Considering the fact that the evidence available to address this question is based on retrospective small case series with heterogenous methodologies, the level of recommendation is moderate at best. Taken as a whole, it appears that single-stage revision for acute PJIs may achieve eradication of infection in approximately 70% of patients, which is superior to many reported rates of success for irrigation/debridement and implant retention in the same setting [6]. Furthermore, this technique limits the perioperative morbidity, surgical complexity and healthcare costs associated with a two-stage exchange arthroplasty, and as such, should be strongly considered in the setting of acute PJIs of a THA.

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QUESTION 4: Does the morbidity and mortality differ between single-stage and two-stage exchange arthroplasty?

RECOMMENDATION: Putting aside the effect on successful treatment of periprosthetic joint infections (PJIs), it is logical that a single surgical procedure puts patients at lower risk for both mortality and morbidity compared to a two-stage exchange arthroplasty that involves two separate operations.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 83%, Disagree: 13%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

PJIs are associated with major patient morbidity and mortality. Browne et al. [1] put this in context with a contemporary comparison of two-stage revision hip arthroplasty to major non-orthopaedic surgery. In their study of over 10,386 patients, implant removal and spacer placementhad a 30-day readmission rate of 11.1% and a 90-day mortality rate of 2.6%. Major complications were found in 15.3% of the patients. Ninety-day mortality rates were significantly higher compared with carotid endarterectomy, prostatectomy and kidney transplant (odds ratio (ORs) between 2.1 and 12.5; $p < .0001$). Readmission rates at 30 days were significantly higher than all other groups including coronary artery bypass grafting and Whipple procedures (ORs between 1.4 and 8.2; $p < .0001$). A recent analysis of a large, prospectively collected, national database has also suggested that revision total knee arthroplasty (TKA) for PJIs is associated with increased postoperative morbidity and mortality in the first 30 postoperative days relative to non-infectious revisions [2].

Traditionally, it has been considered that a two-stage revision strategy may be the gold standardfor the management of PJIs as this allows for a more targeted antimicrobial plan; however, it also exposes the patient to the risks of an additional procedure [3]. Historically, studies have concentrated on the successful eradication of infection as an end-point for comparing one and two-stage surgery. Considering reinfection, several recent systematic reviews have been published that show equivalence in terms of infection eradication for single and two-stage exchange [4–8].

Morbidity

Putting the success of eradication of infection aside, morbidity other than reinfection has generally been rarely reported. Although there are limited qualitative studies that deal with the quality of life of the patients undergoing revision arthroplasty for PJIs, Moore et al. [9] found that deep PJIs impacted all aspects of patients' lives. Two-stage revision had a greater impact than one-stage revision on participants' well-being, because the time in between revision procedures led to long periods of immobility and related psychological distress. However, within the two-stage literature, there is marked difficulty in the interpretation of the data presented and what actually constitutes morbidity for the patient. Gomez et al. [10] raised several important points for discussion, and they highlighted the attrition of patients during the interval period in the two-stage process. Of their 504 cases of PJIs (326 knees and 178 hips), 18% failed to proceed to the second stage. The main reason given was that the patient was unfit for the surgical procedure. Clearly this sub-group represents a major morbidity for the patients concerned and may not be included in other reported results.

With regards to hip surgery, a recent systematic review and meta-analysis published by Kunutsor et al. [6] found that there have been no randomized controlled trials comparing one-stage and two-stage revision hip procedures. All included eligible studies were non-randomized longitudinal cohort studies, which were predominantly retrospective in nature. Very few studies in this systematic review contained morbidity (other than reinfection) as an outcome measure. De Man et al. sought to assess and compare functional outcomes in hip PJIs managed by both strategies [11]. They undertook a retrospective analysis and compared 22 single-stage and 50 two-stage revisions to a control group, who were revised for aseptic loosening. They demonstrated no statistically significant differences in Harris Hip Scores (HHSs), limping and use of support between the single-stage and control groups. Choi et al. performed a retrospective analysis of 17 single-stage and 44 two-stage revisions and found no significance differences in HHS or UCLA activity scores [12]. Klouche et al. found no significant differences in aretrospective analysis of 38 single-stage and 46 two-stage revisions between the two groups in terms of pre- and postoperative Merle d'Aubigné scores or complication rates [13]. Oussedik et al. performed a prospective study comparing 11 single-stage with 39 two-stage revisions and found that the HHS and visual analogue scale satisfaction scores were significantly higher in the single-stage group at a mean of five years postoperatively. They also found that the single-stage patients had a significantly greater improvement in their HHS scores and found that patient satisfaction was also statistically in favor of the single-stage procedure [14]. Reporting of morbidities in the remaining 98 individual studies was too infrequent to draw any significant conclusions.

With regards to knee surgery, the results of another systematic review of 10 single-stage and 108 two-stage studies comprising 5,552 participants also failed to find any studies which used morbidity as a primary outcome measure [5]. Using postoperative clinical outcomes from the studies, neither single- nor two-stage strategies for knee PJIs displayed superiority. Median postoperative range of motion for single-stage revision was 97.5 degrees (range, 93.8 to 100.5 degrees) and for a two-stage revision was 97.8 degrees (range, 93.7 to 104.0). Both median postoperative Knee Society knee scores and Knee Society function scores also showed no statistically significant differences.

Mortality

While clearly mortality is a very definite end-point, the causes for it can be multi-factorial and not always directly attributed to the PJIs and their treatment. When reanalyzing the papers from recent systematic reviews for hip and knee PJIs (with mortality as an outcome), establishing differences between a single- and two-stage approach is extremely difficult [5,6]. A minority of studies featured information about mortality. The upper limit of follow-up duration, where death was considered relevant, or was linked to the revision surgery in the manuscript, ranged from 14 days to 15 years [15,16]. Given that death was rarely a measured outcome, the variation in patient selection (some studies excluded patients who died), the absence of an "unrelated mortality" definition, and the variation in follow-up, meaningful pooled analysis from these studies was not possible. Comparison is also difficult even among studies using one revision strategy: Buchholz et al. found a mortality of 2% (patients) relating to "overall management" with up to nine-year follow-up in 640 single-stage hip revisions [15]. In contrast Raut et al. found an attributable mortality of 0% in their 183 single-stage hip revisions with an "unrelated mortality" of 7.7% (14 patients) [16]. One of the included papers by Wolf et al. used a Markov expected-utility decision analysis for which they derived a mortality rate of 0.52% (3 of 576) for single-stage and 2.5% (8 of 321) for two-stage revision based on 18 published papers [17]. The other reviewed articles were no clearer for two-stage revision or for either strategy in knee PJI revisions. Registry data may be a source of crude mortality; however, the joint registry annual reports of England (including Wales, Northern Ireland and the Isle of Man), Australia, Norway, Sweden, Finland, Canada and New Zealand currently do not publish mortality data for revision subgroups [18–23].

Another method of analyzing mortality rates following single and two-stage exchange, which clearly has some limitations, is to present a data summary of published reports that include 50 or more patients and where mortality is documented (see below). As can been seen in these series, there is marked overlap of the mortality ranges, but the highest mortality is evident with a two-stage exchange. The heterogeneity of the available data is far from robust to undergo meaningful meta-analysis.

One-stage mortality range - 4.4 to 11.4%

Buchholz et al. [24] N = 640 with 90 deaths recorded at mean 52 months follow-up = 8.1%

Loty et al. [25] N = 90 with 4 deaths reported at mean 47 months follow-up = 4.4%

Miley et al. [26] N = 100 with 11 deaths recorded at mean 48.5 months follow-up = 11%

Raut et al. [16] N = 123 with 14 deaths at mean 93 months follow-up = 11.4%

Two-stage mortality range - 2.9 to 25.7%

Chen et al. [27] N = 57 with 5 deaths at mean 67.2 month follow-up = 8.7%

Haddad et al. [28] N = 50with 2 deaths at mean 5.8 years follow-up = 4.0%

Hsieh et al. [29]N = 99 with 3 deaths at mean 43 months follow-up = 3.0%

Romanò et al. [30] N = 102 with 3 deaths at mean 48 months follow-up = 2.9%

Toulson et al. [31] N = 132 with 34 deaths at mean 64.8 months follow-up = 25.7%

Ibrahim et al. [32] N = 125 with 19 deaths at mean 5.8 years follow-up = 15.2%

In conclusion, based on the available studies to date, single-stage revision surgery (when suitable) is associated with lower morbidity and mortality rates. However, the data to support this statement is

weak and larger, prospective, multicenter clinical trials are needed. Of note, two prospective randomized trials are currently recruiting with the aim to compare single- and two-stage revision surgery in the United Kingdom and North America with outcome measures including reinfection, mortality and patient reported outcomes [33].

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5.4. TREATMENT: TWO-STAGE EXCHANGE, SPACER RELATED

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QUESTION 1: What are the indications for the use of non-articulating vs. articulating spacers during resection arthroplasty of the hip or knee?

RECOMMENDATION: Articulating spacers appear to provide better range of motion and less functional limitations to the patients undergoing resection arthroplasty and should be used whenever possible. The indications for the use of non-articulating spacers during resection arthroplasty include patients with major bone loss, lack of ligamentous integrity (knee) or abductor mechanism (hip) that places these patients at elevated risk for dislocation or periprosthetic fracture and patients who have major soft tissue defects in whom motion is protected to allow better wound healing.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 91%, Disagree: 7%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

There is no clear consensus on the ideal type of spacer for management of periprosthetic joint infections (PJIs) of the hip and knee. Articulating spacers have been shown to be associated with improved range of motion, better function and also with the ability to facilitate ease of dissection at the second stage [1–5]. Citak et al. [6] reported superior functional outcomes with the use of articulating spacers when compared to static spacers.

Della Valle and colleagues recently demonstrated in a multicenter randomized controlled trial (American Association of Hip and Knee Surgeons (AAHKS) abstract) that articulating spacers for hip are associated with reduced lengths of hospital stay after both the first and second stage. Furthermore, they demonstrated improved range of motion of the knee at one year in the articulating spacer group (113 vs. 100 degrees ($p = 0.033$)) and a more significant improvement from preoperative and postoperative range of motion (18 vs. 3 degrees($p = 0.045$)).

The cost of articulating spacers as well as complications demonstrated with these have been highlighted [7–10]. However, these studies are heterogeneous and are predominantly retrospective case series. Citak et al. [6] observed that surgeon-made articulating spacers were more likely to fracture compared to preformed spacers despite having equivalent functional outcomes and infection eradication rates.

Dislocation rates of hip articulating spacers have been reported to range from 6.4 - 17.5% [5,7,9,11]. Dislocation was significantly higher in designs without an acetabular component or those implanted without cement in the acetabulum [7]. This finding is likely design related. Biring et al. reported a 3% dislocation rate with the prosthesis with antibiotic-loaded acrylic cement (PROSTALAC) spacer and satisfaction scores of 90.5 points at 10 - 15 years mean follow-ups [12]. A total of 44% of the group treated by Tsung et al. experienced such encouraging results with the custom-made articulating spacer (CUMARS) based on the Exeter stem that they opted to not have the second stage [13]. The incidence of periprosthetic fractures has been reported to be up to 11.4% with the use of mobile spacers [9].

Several authors have attempted to compare the results of static and articulating spacers in the knee [1,2,4,14]. However, there is a paucity of high quality evidence. Choi et al. [15], Johnson et al. [14], Chiang et al. [2] and Park et al. [1] found that non-articulating spacers were associated with more bone loss (in keeping with the conclusion of Della Valle et al.), increased rates of patella baja, lower Knee Society scores and range of motion (ROM) and required the use of more extensile approaches at the time of reimplantation. These studies are mainly case series and likely subject to selection bias, as patients with more important bone loss at the time of resection arthroplasty are also more likely to have undergone revision to a static spacer.

More recently, Faschingbauer et al. [16] reported a 9.1% fracture rate and an overall 15% rate of complications in 133 patients treated with static knee spacers. Lichstein et al. [17] reported a 94% eradication rate (in the presence of 25% drug resistant organisms), 100° median ROM after reimplantation and Knee Society Scores similar to those published in two recent systematic reviews [18,19]. Neither Voleti et al. [19] nor Pivec et al. [18] were able to identify significant differences between articulating ($n = 1,934$) and non-articulating ($n = 1,361$) spacers with respect to eradication of infection, complication rates or knee function following implantation. The former study [19] did, however, identify improved knee motion among patients with articulating spacers.

The current evidence does suggest improved function, better patient satisfaction and reduced lengths of hospital stay when an articulating spacer is used during resection arthroplasty compared to non-articulating spacers. In the absence of high level data, we recommend that articulating spacers be used in patients undergoing resection arthroplasty whenever possible. There are, however, circumstances when an articulating spacer is not likely to function well, which include patients with a lack of collateral ligaments in the knee,or with absent abductor mechanisms in the hip. These circumstances place these patients at increased risk for spacer dislocation. In addition, massive bone loss may also preclude the use of articulating spacers as fixation of the spacer may be suboptimal in the first place or its use may result in an elevated risk for periprosthetic fracture. There are also other circumstances when surgeons prefer to immobilize the joint with the use of a non-articulating spacers, which may allow for better healing of the wound.

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QUESTION 2: What are the indications for interim cement spacer exchange or repeat irrigation and debridement (I&D) instead of reimplantation?

RECOMMENDATION: Interim cement spacer exchange and/or repeat I&D may be performed, instead of reimplantation, in the presence of persistent infection and/or mechanical complications.

LEVEL OF RECOMMENDATION: Limited

DELEGATE VOTE: Agree: 97%, Disagree: 0%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

Two-stage exchange arthroplasty remains the most utilized surgical treatment for the treatment of chronic periprosthetic joint infections (PJIs). However, there are occasions when the antibiotic cement spacer may be exchanged, or an I&D performed, and the reimplantation delayed [1]. The reason for these additional surgical procedures may include the inability to control infection or when potential infection is encountered during an intended reimplantation.

The rationale behind this spacer exchange practice is to deliver a further "new load" of local antibiotics as a strategy to treat the persistent infection [2,3]. Alternatively, an I&D at this stage is hypothesized to reduce the microbial bioburden. Although these practices seem intuitively rational, there is little to no published literature on the outcomes of interim spacer exchanges or additional irrigation and debridement. These additional procedures also carry marked morbidity and affect the patient journey, with Gomez et al. reporting that 17.3% of these patients never undergo reimplantation and 11.9% require more than one spacer [1]. It therefore remains unknown whether interim spacer exchange confers any benefit versus conventional two-stage exchange or in comparison to altered inter-stage antibiotic treatment.

George et al. recently presented a series of 416 two-stage exchanges for PJIs, of which 59 (17%) had an interim spacer exchange performed [4]. On assessment of Delphi treatment success, two-year and five-year success rates were 77% and 66% in the exchange group versus 86% and 77% in the non-exchange group. Their spacer exchange group had a lower infection-free survival adjusted hazard ratio (aHR) 10.69, 95% confidence interval (CI) 1.02-2.81; p = 0.039. Similar findings were presented by Goswami et al. in a retrospective study of 75 interim spacer exchanges and 352 matched controls undergoing conventional two-stage exchange at mean 3.5-year follow-up [5]. They found 31.1% of the interim exchange cohort failed treatment after eventual reimplantation, with a significantly lower treatment success compared to matched patients who underwent conventional two-stage exchange (p = 0.045).

Current indications for an additional spacer exchange or I&D include persistent infection, wound-related problems, draining sinus or mechanical complications such as spacer dislocation or fracture. However, there is also no gold standard diagnostic method demonstrating eradication of joint infection or for optimal timing of reimplantation. Several studies have identified metrics that are useful in determining if there is a persistent infectious state prior to reimplantation. Histological analysis, synovial fluid cell counts, serum D-dimer, leukocyte esterase (LE), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have all been investigated [6–12].

Feldman et al. evaluated the ability of frozen section histology to identify ongoing infection [13]. They concluded that >5 polymorphonuclear (PMN) cells per high power field (HPF) had 100% sensitivity and 96% specificity for the detection of infection. On the contrary, in a cohort of 54 patients, Cho et al. evaluated the role of PMN cell count in frozen sections at reimplantation in total knee arthroplasties (TKAs) [12]. They identified 15 patients with 5 to 20 PMNs per HPF during reimplantation. At a minimum follow-up of two years, they reported 100% eradication of infection, casting doubt on the role of frozen sections. Furthermore, George et al. demonstrated limited utility of this method for ruling out infection, given a sensitivity of only 50% (CI, 13 - 88%) [14]. False-positive frozen section results can potentially arise in patients with the use of dynamic spacers in hips, which may result in debris that accentuates inflammation seen in frozen sections, thereby making conclusions from frozen section, unreliable in such scenarios.

ESR, CRP and joint aspiration have also been evaluated in this context [8,15]. However, there is no convincing evidence to establish their roles in diagnosing persistent infection or in determining if reimplantation is indicated. Ghanem et al. attempted to define cut-off values for ESR and CRP that improve clinical differentiation between aseptic failure and periprosthetic infection prior to revision total hip arthroplasty [16]. They published that an ESR threshold of 30 mm/h has a sensitivity of 94.3% and a CRP threshold of 10 mg/L had a sensitivity of 91.1% for infection. When combining ESR and CRP cut-offs for a positive diagnosis, this increased the sensitivity to 97.6%. However, when calculated by receiver operating curve (ROC) analysis, the predictive cut-offs equated to 31 mm/h for ESR and 20.5 mg/L for CRP.

Zmitowski et al. evaluated 129 patients undergoing two-stage arthroplasty who had an aspiration before their second-stage procedure [6]. Persistent infection was defined as a positive aspirate culture. In 33 cases (25.6%) that were classified as persistent PJIs, patients had significantly elevated PMN % (62.2 vs. 48.9%; p = 0.03) and white blood cell (WBC) counts (1,804 vs. 954 cells/μL; p = 0.04). Although statistically significant differences were noted, diagnostic accuracy for persistent PJIs was <60% for all variables, except synovial WBC counts.

In another retrospective study of 76 infected TKAs treated with two-stage exchange, Kusuma et al. evaluated the role of serological tests for determining eradication of infection during two-stage exchanges [8]. They concluded that while the ESR, CRP and synovial fluid WBC count decreased in cases where infection control was achieved, these values frequently remained elevated. The ESR remained persistently elevated in 54% of knees and the CRP remained elevated in 21% of knees where the infection had been controlled. Despite their inability to identify any patterns in these tests indicative of persistent infection, they proposed that synovial fluid WBC counts as the best test for confirmation of infection control.

Furthermore, Janz et al. investigated the effectiveness of synovial aspiration in resection arthroplasty hips for detecting persistent infection in patients undergoing two-stage revision total hip arthroplasty (THA) [10]. Diagnostic performance of the synovial aspiration

of these hips achieved a sensitivity of only 13% and a specificity of 98%. They concluded that aspiration is of limited diagnostic validity and cannot reliably detect or rule out infection. However, they highlighted the fact that a positive aspiration culture had a high diagnostic performance.

Recently, serum D-dimer tests have been proposed as promising tests for diagnosing PJIs [7]. The study evaluated the role of D-dimer in detecting the presence of infection at the time of reimplantation. Out of five patients with raised D-dimer levels at the time of reimplantation, two had a positive culture from samples taken during reimplantation and subsequently failed. It is worth mentioning that both ESR and CRP values were normal in these two patients.

As previously mentioned, there is no gold standard test for PJIs. After spacer insertion and a period of antibiotic treatment, infection control is expected and laboratory and clinical signs are expected to improve.

In the setting of a failure to improve or if there is ongoing active infection at the time of planned reimplantation, a repeated irrigation, debridement and spacer exchange may be considered. Further research is essential to establish effective tests that prove eradication of PJIs and therefore determine if reimplantation should be performed. The role of several tests, such as elevated ESR and CRP, synovial WBC, and PMN % as well as serum D-dimer are helpful in determining whether reimplantation can be carried out but are not absolute determinants. A combination of these tests, clinical suspicion, completion of antibiotic therapy and careful evaluation of MusculoSkeletal Infection Society (MSIS) criteria [17] should be used to determine if a repeated cement spacer exchange may be indicated. Repeated I&D of an implanted spacer, without antibiotic spacer exchange, does not seem to have any evidence and is generally considered a suboptimal approach in this setting.

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QUESTION 3: Should the antibiotics placed in a cement spacer be tailored to the sensitivity of the infective organism?

RECOMMENDATION: Antibiotics added to cement spacer during resection arthroplasty should be tailored towards the causative organism and its susceptibility. In case of culture negative periprosthetic joint infections (PJIs), consideration should be given to the addition of a broad-spectrum antibiotic to the cement spacer to cover the most potential pathogens causing PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 94%, Disagree: 3%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

The literature was reviewed to identify all publications related to the above question. The systemic review revealed 12 publications with clear information about tailored local antibiotics in bone cement spacers. The majority of the papers were retrospective studies with a relatively low number of patients in each report. One study by Hsieh et al. contained 99 patients, which was the largest cohort [1]. There were two review articles from the same group [2,3]. Kiniet al. reviewed the available literature that consisted of 17 publications related to hip infections and 18 studies related to PJIs of the knee. They did not find clear evidence related to the issue of antibiotics

added to cement, but believed that the literature is supportive of the concept that the antibiotics added to cement should be tailored towards the causative organism, if preoperative cultures were successful in isolating the infecting organism and determining the antibiotic susceptibility [2]. Sukeik et al. concluded that the type of local antibiotics added to the cement or otherwise should be safe, thermostable, hypoallergenic, water soluble, have an adequate bacterial spectrum and be available as a sterile powder [3]. Kooet al. also suggested that antibiotics selected for cement spacer delivery should correspond to the sensitivity of the pathogens and be thermostable [4]. Nevertheless, novel delivery techniques may overcome this problem by microencapsulating antibiotics in alginate beads without affecting elution, handling properties and mechanical strength of the cement [5].

Even though there are no recommended diagnostic protocols adequate to exclude infection persistence prior to reimplantation, blood tests and synovial fluid aspiration before surgical treatment of PJIs can be helpful [2,3,6–10]. Aspirates are cultured and the results of microbiological diagnostics, including the causative organism and the specific antibiotic sensitivity, determine the treatment strategy where consultation of a microbiologist plays a crucial role [1,4,6,11–16].

Local antibiotic concentration at the site of infection can far exceed those obtained by systemic antibiotics alone and can remain well above therapeutic requirements for a longer period of time [1]. The objective is to deliver a high concentration of local antibiotics against the causative pathogens [2]. The choice of antibiotics is based on results of bacterial culture obtained from the preoperative aspiration or tissue specimens from around the joint [1,13,16]. Once the antibiotic susceptibility profile of the microorganisms is analyzed, a designated microbiologist should prepare a specific tailored combination of local antibiotics for use in the bone cement spacer [6], considering the patient allergy profile and medical conditions, particularly renal function [17,18]. If the infective organism cannot be identified preoperatively or infection is identified during a presumed aseptic revision, then a broad-spectrum empiric combination of antibiotics is used in an attempt to avoid development of resistance [1,2,13,15,19]. We have provided a list of all available antibiotics, the range of doses to be used in cement spacers and the organisms that they can target (Table 1).

TABLE 1. Available antibiotics and anti-fungals which can be used in spacers

Antibiotic Group	Type of Antibiotic	Activity Against	Dose per 40 gm cement (in grams)
Aminoglycoside	Tobramycin	Gram-negative bacteria such as *Pseudomonas*	1 to 4.8
Aminoglycoside	Gentamicin	Gram-negative bacteria-*Escherichia coli, Klebsiella* and particularly *Pseudomonas aeruginosa.* Also aerobic bacteria (not obligate/ facultative anaerobes)	0.25 to 4.8
Cephalosporin, 1st gen	Cefazolin	Gram-positive infections, limited gram-negative coverage	1 to 2
Cephalosporin, 2nd gen	Cefuroxime	Reduced gram-positive coverage, improved gram-negative coverage	1.5 to 2
Cephalosporin, 3rd gen	Ceftazidime	Gram-negative bacteria, particularly *Pseudomonas*	2
Cephalosporin, 4th gen	Cefotaxime	Gram-negative bacteria, no activity against *Pseudomonas*	2
Cephalosporin, 5th gen	Ceftaroilne	Gram-negative bacteria, no activity against *Pseudomonas*	2 to 4
Fluoroquinolone	Ciprofloxacin	Gram-negative organisms including activity against *Enterobacteriaciae*	0.2 to 3
Glycopeptide	Vancomycin	Gram-positive bacteria, including methicillin-resistant organisms	0.5 to 4
Lincosamide	Clindamycin	Gram-positive cocci, anaerobes	1 to 2
Macrolide	Erythromycin	Aerobic gram-positive cocci and bacilli	0.5 to 1
Polymyxin	Colistin	Gram-negative	0.24
β-lactam	Piperacillin-not available Piptzobactam	Gram-negative bacteria (particularly *Pseudomonas*), Enterobacteria and anaerobes	4 to 8
β-lactam	Aztreonam	Only gram-negative bacteria	4
β-lactamase inhibitor	Tazobactam	Gram-negative bacteria (particularly *Pseudomonas*), Enterobacteria, and anaerobes in combination with Piperacillin	0.5
Oxazolidinones	Linezolid	Multidrug-resistant gram-positive cocci such as MRSA	1.2
Carbapenem	Meropenem	Gram-positive and gram-negative bacteria, anaerobes, *Pseudomonas*	0.5 to 4
Lipopeptide	Daptomycin	Only gram-positive organisms	2
Antifungale	Amphotericin	Most fungi	200
Antifungal	Voricanazole	Most fungi	300-600 mg

One study suggested that the custom-made cement spacer that contains specific antibiotics targeted towards the infective organism(s) should be made after consultation with a microbiologist or infectious disease specialist [6]. Antibiotics like gentamicin, vancomycin, ampicillin, clindamycin and meropenem can be used as a combination based on organism susceptibility [4,6,14]. Even in cases of multi-resistant germs like methicillin-resistant *Staphylococcus aureus*/methicillin-resistant *Staphylococcus epidermidis* (MRSA/MRSE), it was possible to achieve a 100% infection control rate when the local antibiotic therapy was tailored towards the infecting organism(s) [11]. It is, however, a known fact that antibiotic elution from spacers decreases over time. Studies have shown that bacterial colonization of spacers can occur with increasing in situ time [18,20–22]. Antibiotic cement spacers, thus, play a role for a finite period of time and should be removed at some point.

Another question that remains is whether antibiotics should be added to cement, if used, during reimplantation surgery and, if added, whether the antibiotics should be tailored towards the infective agent. This question has been answered comprehensively elsewhere in the consensus document, citing all the supportive literature. It is, however, our opinion that the addition of targeted antibiotics to cement, if used during reimplantation, may also play a role in reducing the incidence of subsequent failure.

In conclusion, based on a review of the available evidence, it is recommended that the type of antibiotics added to the cement spacer should be targeted towards the infective organism(s) and their susceptibility as determined by preoperative culture. In cases of culture-negative PJIs, strong consideration should be given for the addition of broad-spectrum antibiotics to cement spacers that have activity against the most common organisms causing PJIs.

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QUESTION 4: Which antibiotic(s) should be added to a cement spacer in patients with periprosthetic joint infections (PJIs) caused by multiresistant organisms?

RECOMMENDATION: In the case of PJIs caused by methicillin-resistant *Staphylococcus* aureus/methicillin-resistant *Staphylococcus epidermidis* (MRSA/MRSE), vancomycin should be added to the bone cement spacer. In vancomycin-resistant strains, such as vancomycin-resistant Enterococcus (VRE), or in multiresistant gram-negative PJI cases, individual decision making is mandatory based on the known susceptibilities. Consultation with a microbiologist/infectious disease specialist is strongly recommended.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 99%, Disagree: 0%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Multidrug resistant (MDR) pathogens in the context of periprosthetic joint infections (PJIs) are MRSA, MRSE or VRE and multidrug-resistant gram-negatives (MRGN).

Most PJIs are caused by gram-positive cocci, including *Staphylococcus* species [1], and in some reports methicillin-resistant organisms account for up to 74% of PJIs [2]. For the treatment of PJIs caused by MRSA, vancomycin is usually used for antibiotic therapy and commonly incorporated into bone cement as well as intravenous treatment [3]. The successful clinical control of chronic PJIs due to methicillin-resistant organisms varies from 48 - 89% [4,5] in the hip and 60 - 74% [6,7] in the knee when vancomycin is used in two-stage exchange arthroplasty.

The optimal combination of antibiotics in polymethyl methacrylate cement is not known. Most surgeons prefer to add between two to four grams of vancomycin and a similar dose of an aminoglycoside, such as gentamicin or tobramycin, to the cement. The addition of dual antibiotics to cement has several advantages including a postulated synergy between vancomycin and gentamicin against gram-positive bacteria [8,9] and an improved antibiotic elution from the spacer [10,11]. Moreover, this antibiotic combination results in a decreased risk of bacterial growth on the surface of the cement spacer, which could be detrimental to thecontrol of the infection [10]. Systemic toxicity as a result of elution of antibiotics from cement spacers, though rare, can occur. Thus, it is important to ensure that the renal clearance of the patient and the viscosity of the cement, which affects antibiotic elution, is considered when forming the spacer during resection arthroplasty. Renal toxicity of vancomycin is a potential risk and renal function should be monitored [11,12]. However, Hsieh et al. noted no systemic adverse effects after using high doses of vancomycin and aztreonam in bone cement in 46 patients with a PJI of the hip [13]. Also, Springer et al. reported no systemic adverse effects from the use of high doses of vancomycin and gentamicin in cement spacers in a series of 36 knees with PJIs [14].

Regarding susceptible gram-negative bacteria, third-generation cephalosporins [15], carbapenems [16–19] and monobactam antibiotics [13] have strong activity. They retain their antibacterial capacities after being added into bone cement, but they exhibit different antibacterial durations even when the same antibiotic dose has been used. The kinetics of antibiotic release from bone cement depends on the penetration of dissolution fluids into the polymer matrix and subsequent diffusion of the dissolved drug from the cement [20]. Consequently, the limiting factor that determines the antibacterial activity of the cement is the efficiency of antibiotic elution.

The published literature on the topic of what antibiotics should be added to cement spacers for management of PJIs caused by resistant organisms is not well-established. A few reports exist related to management of PJIs caused by MRSA and MRSE with less literature related to the management of PJIs caused by multi-resistant gram-negative organisms. Numerous factors need to be considered when adding antibiotics to cement, including the renal function of the host, the antibiogram of the organism, the type of cement being used, the allergy profile of the host and so forth. In addition, other patient comorbidities, duration and type of intravenous/oral (IV/PO) antibiotics after spacer placement and the quality of bone and soft tissues should be taken into consideration.

The objective of adding antibiotics to cement spacers is to allow for high elution of antibiotics into the affected joint that will reach beyond the organism minimum inhibitory concentration while avoiding potential for systemic drug toxicity [14,21]. It is important to note that on occasion alternative antibiotics may be added to cement spacers based on the allergy profile of the patient.

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QUESTION 5: What are the contraindications to using antibiotics in a cement spacer?

RECOMMENDATION: With the exception of a scenario in which a patient has a history of severe adverse reaction to each of the thermally-stable antibiotics intended for use in cement spacers in the treatment of prosthetic joint arthroplasty, there are no definite contraindications to using antibiotics in a cement spacer.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 90%, Disagree: 6%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

There are no prospective studies directly comparing the use of cement spacers with and without antibiotics. A small randomized controlled trial by Cabrita et al. assessed patients with vancomycin-loaded spacers versus no spacers [1]. The infection rate and multiple outcomes were significantly improved with the use of an antibiotic-loaded spacer; however, it is impossible to separate benefits of the presence of the spacer versus impregnation of the spacer with antibiotics. A retrospective assessment of 120 cases found no benefit in infection eradication with the use of an antibiotic-loaded spacer but also noted no adverse effects from their use [2].

There are no studies that describe a benefit from omitting antibiotics from the cement spacer used to treat infection.

There are multiple case reports relating to nephrotoxicity associated with the use of aminoglycosides and other antibiotics [3–13]. Recommendations include monitoring renal function and other clinical parameters and consideration of spacer removal as soon as possible in the case of ongoing renal dysfunction. Of all of these reports, two papers recommend avoiding aminoglycoside antibiotics in patients at risk of developing renal impairment [12]. Infection has been acknowledged as a risk factor in renal impairment and the relative contributions are unknown. Hypersensitivity to piperacillin/tazobactam has also been observed [14]. Vancomycin has also been associated with systemic adverse reactions when included in the cemented spacers [10,15]. This suggests that specific antibiotics may need to be avoided in the cement spacer on a case-by-case basis, but it does not suggest that antibiotics should be avoided in their entirety.

With the exception of a history of life-threatening allergic reaction to a specific antibiotic [15], no published studies or reports are recommending an outright contraindication to the addition of antibiotics to the cement of a spacer in the treatment of infection. There is a hypothetical scenario of a patient who has a history of severe adverse reactions to each of the thermally-stable antibiotics described for use in cement spacers in the treatment of prosthetic joint arthroplasties that could constitute a contraindication.There are no published case reports of this scenario.

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QUESTION 6: Does the use of surgical drains reduce the effectiveness of antibiotic-impregnated cement spacers?

RECOMMENDATION: The current literature indicates that the use of surgical drains does not reduce the overall effectiveness of antibiotic-impregnated cement spacers.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 85%, Disagree: 10%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Recent literature suggests there is no inherent benefit to using closed suction drainage (CSD) following primary total joint arthroplasty (TJA) [1–3]. Additionally, many of these studies have concluded that CSD is costly and can negatively influence early functional outcomes in primary TJA patients [4]. However, the utility of CSD in revision TJA has yet to be determined. In contrast to primary TJA, revision TJA has been shown to result in greater blood loss as well as increased wound complications and hematoma formation because of its greater operative complexity [5]. The potential value of using CSD for revision TJA lies in the belief that lowering the tamponade-like effect of hematoma formation may lead to improved wound healing and better functional outcomes. A randomized prospective study comparing groups with CSD and those without CSD demonstrated no significant differences in patient satisfaction, pain levels and early functional outcomes for patients undergoing aseptic revision [6]. Still, there is much debate in regards to how CSD plays a role in periprosthetic joint infections (PJIs) following revision TJA and whether CSD should be used when there is placement of an antibiotic-laden cement spacer.

The influence of CSD on local antibiotic concentrations following cement spacer placement is not well-studied. In 2006, Hsieh et al. reported on a series of 46 patients who underwent two-stage hip revisions. Drains were placed for seven days and used to measure antibiotic levels (vancomycin) from day one to seven [7]. A comparison was made between serum antibiotic levels and antibiotic levels in the affected joint at a mean of 107 days postoperatively following the first-stage surgery. Antibiotic concentrations were noted to be above the minimal required level showing substantial elution despite drain placement. Again in 2009, Hsieh et al. assessed the drain fluid of 42 patients who had gentamicin spacers following infected total hip arthroplasty. They concluded that antibiotic levels in the drain fluid were also at clinically effective levels [8].

In 2009, Anagnostakos et al. reported on a series of 28 patients who had infected total hip arthroplasties. Hip spacers were used in 17 patients and beads were used in 11 patients. Drains were placed until there was less than 50mL of daily output and local concentrations of vancomycin and gentamicin were assessed at that time. The study showed that that beads showed better elution rates than spacers after drains [9]. This may have been the result of increased surface area when using beads as the vector for antibiotic elution. Additionally, a study by Regis et al. examined seven patients who had infected total hip arthroplasties. Drains were placed for 24 hours and drainage fluid was obtained at 1 and 24 hours, respectively. Antibiotic concentration and bactericidal titers were analyzed against staphylococcal strains. Vancomycin and gentamicin concentrations were bactericidal at 1 and 24 hours, showing that the drains had not reduced the efficacy of elution [10]. Similarly, Balato et al. enrolled 18 patients in a prospective study where 10 total hip and 8 total knee arthroplasty patients underwent two-stage revisions with the placement of drains for 48 hours. Samples were collected at 15 intervals over the course of the 48-hour period. Antibiotic concentrations were highest at 1 hour and lowest at 48 hours. However, bactericidal concentrations of antibiotics were found at 48 hours, providing evidence of effective elution after drain placement [11].

Additionally, a study by Bertazzoni et al. reported similar findings to those mentioned above. They used drains to measure the concentrations of a vancomycin and gentamicin combination spacer in 12 patients for a 24-hour period following revision hip and knee arthroplasty [12]. They concluded that the concentrations of gentamicin and vancomycin were bactericidal, exerting a strong inhibitory effect against methicillin-resistant *Staphalococcus aureus* and coagulase-negative staphylococci strains. This demonstrated that drains had not reduced the efficacy of the antibiotic spacer elution rates. Another study by Isiklar et al. reported similar findings for spacers with vancomycin alone [13]. Kelm at al. used a novel study design (using both in vivo and in vitro analysis) to examine the spacers of ten patients who had infected total hip arthroplasties [14]. Initially, spacers were implanted and drain fluid was assessed every 24 hours for 7 days. Spacers were explanted at a mean of 9 weeks and they were analyzed for antibiotic concentrations left over. It was determined that after explantation there was still a sufficient concentration of antibiotics to inhibit bacterial growth even after drain placement for up to 7 days. In contrast, further research using animal models, where drains can be left in place for much longer, have measured antibiotic release up to 7 weeks [15].

The above studies illustrate that the presence of a drain does not diminish the minimal bactericidal concentration of antibiotics eluted from an implanted antibiotic-laden spacer. There was no evidence available to support a claim that the presence of drains increased the risk of reinfection. However, in a retrospective review of 82 patients who underwent two-stage revisions, Jung et al. noted that increased drain output was an independent risk factor for prolonged wound drainage and this indirectly was a significant predictor of wound infection [16].

In summary, although suction drains will remove joint fluid and therefore remove antibiotics from the joint, this is probably only a proportion of the total eluted antibiotic. Once the drains have been removed altogether, elution should continue locally at effective levels as justified by the aforementioned studies.

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QUESTION 7: Is there a role for intraoperative autoclaving and reuse of an infected prosthesis as a spacer during resection arthroplasty?

RECOMMENDATION: Multiple studies have demonstrated that the reuse of autoclaved prosthetic components during knee resection arthroplasty did not compromise the eradication of an established infection. Though a viable option, there are potential legal implications associated with the reuse of autoclaved components and a proper standard for autoclaving of these components is also not known. Reuse of autoclaved components in resection arthroplasty, particularly for the knee, may be suitable in scenarios when proper dynamic spacer components are not available or for economic considerations.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 82%, Disagree: 12%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

There are multiple types of antibiotic spacers reported in the literature. They are intended to preserve potential space for later reimplantation and to deliver high dose local antibiotics from the cement. Spacers are either static or dynamic. Dynamic spacers allow for motion in the hip and knee, limb length preservation in the hip and at least partial weight bearing during the treatment period. Dynamic hip and knee spacers may be constructed from new components, cement molds, or from autoclaved components matched to new tibial or acetabular inserts. The literature on static vs. dynamic knee spacers is mixed, but there is some evidence that eventual range of motion may be superior with the use of dynamic spacers [1].

The reuse of an autoclaved femoral component (AC-FC) as a spacer in prosthetic knee infections was first described by Hofmann et al. [2]. The clinical data from several subsequent studies supports the reuse of an AC-FC (Table 1), though they are Level III to IV evidence studies and are subject to being underpowered. Hofmann et al. reported on a 2- to 12-year experience using an AC-FC, demonstrating that 44 of 50 patients (88%) had successful reimplantation and were infection-free at latest follow-up [2]. Lee et al. reported that 19 of 20 patients were successfully treated using an AC-FC articulating against antibiotic cement [3]. Anderson et al. reported 25 consecutive knees treated with an AC-FC spacer and found a 4% failure rate with excellent motion and knee scores at final follow-up [4]. Emerson et al. compared patients treated before 1995 with a static cement spacer to patients treated after 1995 with an AC-FC dynamic spacer [5]. At final follow-up, the patients with AC-FC achieved a significantly better mean range of motion (107.8 vs. 93.7°), while there was no statistical difference in reinfection rate: 9% for AC-FC vs. 7.6% for static spacers. Chen et al.reported on a series of 18 patients: 10 treated with AC-FC and 8 treated with static cement spacers [6]. Similar to Emerson et al., they reported better eventual mean range of motion in the AC-FC group (94.5°) vs. the static cement spacer group (74.3°), with no statistical difference in reinfection rate. Jämsen et al. presented a retrospective series of 34 knees: 24 treated with AC-FC and 10 treated with cement spacers that were manually molded [7]. The authors described slightly better functional scores with AC-FC without increasing the risk for reinfection. Kalore et al. reported on a retrospective comparison of AC-FC vs. new femoral components and polyethylene vs. molded cement components in 53 patients [8]. The infection control rates were 66%, 87.5% and 63%, respectively, a difference that was not statistically different in this relatively small sample size. Importantly, the implant cost for the AC-FC group averaged $932 compared to about $3,500 for the other two groups.

To our knowledge, there is only one study on reuse of hip components in resection arthroplasty. Etienne et al. first reported the surgical technique to reimplant the autoclaved femoral stem or

TABLE 1. Summary of clinical studies

Study	Number of Knees	Autoclaving Protocol	Type of Femoral Component	Type of Tibial Insert	Follow-up Mean (Range)	Reinfection
Emerson [5]	48 Knees Study Group (AC spacer): 26 Control Group (Static spacer): 22	AC of FC (undetailed protocol)	Metal-on-PE cemented spacer	New PE insert	Study: 3.8 years (2.6-6.4) Control: 7.5 years (2.8-12.7)	Study: 2/26 (7.7%) Control: 2/22 (9%)
Cuckler 2005 [14]	44 Knees	AC of FC and PE insert for 10 minutes	Metal-on-PE cemented spacer	Autoclaved PE insert	5.4 years (2-10)	1/44 (2.27%)
Hofmann 2005 [2]	50 Knees	AC of FC (undetailed protocol)	Metal-on-PE cemented spacer	New PE insert	73 months (24-150)	6/50 (12%)
Huang 2006 [15]	19 Patients (21 Knees)	AC of FC and PE insert (undetailed protocol)	Metal-on-PE cemented spacer	Autoclaved PE insert	52.2 months (30-102)	1/21 (4.76%)
Jämsen 2006 [7]	32 Knees Study Group (AC Spacer):22 Control Group (Static Spacer):8	AC of FC and PE insert (undetailed protocol)	Metal-on-PE cemented spacer	Autoclaved PE insert	Study: 25 months (2–68) Control: 49 months (2-86)	Study: 2/22 (9%) Control: 2/8 (25%)
Pietsch 2006 [16]	33 Knees	AC of FC and PE insert (undetailed protocol)	Metal-on-PE cemented spacer	Autoclaved PE insert	28 months (12-48)	3/33 (9%)
Anderson 2009 [4]	25 Knees	NA	Metal-on-PE cemented spacer	New PE insert	54 months (24-108)	1/25 (4%)
Kalore2012 [8]	53 Knees Study group (AC Spacer): 15 New FC and PE insert (NFC): 16 Cement-on-Cement (SMCs): 22	FC scrubbed with betadine, then AC (undetailed protocol)	Metal-on-cement spacer	-	39 months Study: 73 months (37-105) NFC: 19 months (12-32) SMC: 32 months (14-56)	Study: 2/15 (13.3%) NFC: 1/16 (6.25%) SMC: 2/22 (9%)
Kim 2013 [17]	20 Knees	AC of FC at 137°C for 7 minutes	Metal-on-PE cemented spacer	New PE insert	22.3 months (14-60)	2/20 (10%)
Lee 2015 [3]	19 Knees	AC of FC at 132°C for 30 minutes	Metal-on-cement spacer	-	29 months (24-49)	1/20 (5%)
Chen 2016 [6]	18 Knees Study Group (AC Spacer): 10 Control Group (Static Spacer): 8	AC of FC at 137°C for 7 minutes	Study Group: Metal-on-cement spacer Control: Static Spacer	-	Study: 32 months (24-46) Control: 40.8 months (25-56)	Study: 2/10 (20%) Control: 1/8 (15%)

AC, autoclave; FC, femoral component; PE, polyethylene; SMCs, Silicon molded compnents

an inexpensive femoral stem with a new acetabular liner [9]. They published excellent results in 31 of the 32 patients; however, information on the number of patients receiving a resterilized stem and details of the autoclaving protocol were lacking.

There are questions about the ultimate sterility of autoclaved components because of the few studies directly examining the technique. Lyons et al. cultured swabs from six explanted femoral components both before and after a 45-minute autoclave cycle at 121°C [10]. Autoclaving was able to kill the majority of multiple bacterial species of both the planktonic and biofilm phenotypes on the surface of smooth cobalt and chromium (CoCr) material. The six sterile components were then inoculated with various organisms and the tests were repeated; again, no organisms grew after autoclaving. Additionally, electron microscopic analysis of the inoculated specimens demonstrated a dramatic decrease in biofilm after autoclaving. However, the study used relatively immature biofilms (only 24 hours of growth), whereas biofilm formation in vivo likely occurs over multiple days, if not months, on an implant surface. Leary et al. reported that autoclaving at 121°C for 30 minutes was not able to remove biofilms of *Staphylococcus aureus* or *Staphylococcus epidermidis* from the surface of CoCr discs, but that pre-treatment with a 4% chlorhexidine gluconate scrub brush did successfully remove all biofilm [11]. Additionally, in a more recent study, Williams et al. evaluated different flash autoclave temperatures and durations to remove monomicrobial and polymicrobial biofilms of eight days of maturation [12]. Although ten minutes of autoclaving at 132°C rendered all biofilm nonviable by culture, residual biofilm did remain on the titanium materials studied. The clinical importance of remaining nonviable biofilm is unclear, especially when translating these results from titanium material to the CoCr implants used with AC-FC. The use of 4% chlorhexidine gluconate scrub, as shown by Leary et al., may solve this potential problem [11].

All series in this area are small and subject to Type II error; however, the clinical literature taken as a whole consistently suggests equivalent infection eradication between the different strategies, including use of an AC-FC. Additionally, the laboratory study by Lyons et al. demonstrates the effectiveness of autoclaving at a microbiological and microscopic level [10] and the addition of a chlorhexidine scrub prior to autoclaving may further eliminate the potential for nonviable biofilm remnants [11]. While the available clinical evidence and cost-effectiveness of AC-FC make it an intriguing treatment option, many hospitals are restricting the reimplantation of hip and knee components after autoclave resterilization. The Centers for Disease Control and Prevention (CDC), Association of perioperative Registered Nurses (AORN), health care institutions, implant companies and medical consultation teams are understandably hesitant to temporarily reuse implants for medical, legal and financial reasons [10]. In 2016, a directive released by the Department of Veterans Affairs stated that nonbiological implantable devices are not to be sterilized by flash autoclave and should be used primarily in cases of emergency [13]. Given these restrictions, the AC-FC technique may be most appropriately utilized when proper dynamic spacer components are unavailable or when economic circumstances make it necessary. Future studies to standardize sterilization protocol and spacer techniques with larger patient series should be performed.

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QUESTION 8: Is it necessary to revise or reduce dislocated articulating antibiotic spacers?

RECOMMENDATION: Unless the spacer is pressing against the skin with imminent necrosis/ulceration, resulting in severe, progressive loss of essential soft tissue or bone, neurovascular compromise or notable pain and disability for the patient, a dislocated or fractured antibiotic-impregnated cement spacer is safe to leave in place until definitive second-stage surgery.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 89%, Disagree: 8%, Abstain: 3% (Super Majority, Strong Consensus)

TABLE 1. Summary of studies reporting complications of hip and knee antibiotic cement spacers in the literature

Lead Author	Year	N	Age (Y)	M/F	BMI (Kg/m2)	[1° -2° T] (D)	Follow-up (M)	Complications	Treatment
Lau	2016	72 knees	70,2 ± 1,8	45/26	32,4 ± 6,4	128,2 ± 80,8	44,9 ± 29,8		If subluxation of the articulating spacer is present, constrained revision knee systems as well as augments should be available at time of re-implantation.
Faschingbauer	2015	133 knees	70,1 ± 9,9	69/64				Fracture/fissure of the tibia (n9 - 6,8%); fracture/fissure of the femur (n3 - 2.3%); spacer fracture (n1 - 0,8%); subluxation of the patella (n1 - 0, 8%)	Not clear in the article.
Faschingbauer	2014	138 hips	69,3 ± 10, 5	Spacer fracture (n12 - 8,7%) 50% with a spacer fracture showed a stable condition. The other half underwent spacer revision. Periprosthetic femoral fracture (n1 - 0,7%) Managed Operatively Dislocation with a simultaneous spacer fracture (n1 - 0,7%) Not clear in the article				Dislocation (n12 - 8,7%)	Close reduction and stable retention in 4/12 dislocations. All other underwent spacer revision.
Jung	2009	88 hips	70	43/39		90	54	Dislocations (n15 - 17%)	12 patients >> conservatively by reduction and immobilization in a hip orthesis. The others: in one case (combined spacer dislocation and fracture) >> spacer exchange, two cases (recurrent spacer dislocations and unsuccessful conservative treatment) >> resection arthroplasty.
								Spacer fracture (n9 - 10,2%)	7 (in the distal part of the spacer stem) >> asymptomatic. The other two cases (spacer-neck fractures) >> spacer exchange.
								Periprosthetic femoral fracture (n12 - 13,6%)	4 with femoral scissure >> conservatively; 5 at 1st stage >> implantation of antibiotic-coated femoral nail and spacer implantation on top; 1 (avulsion of the minor trochanter) >> cerclage refixation; 1 fracture beneath the spacer stem >> implantation of an antibiotic-coated prosthesis stem and placement of a spacer head onto the stem.

RATIONALE

Antibiotic-impregnated cement spacers are used after resection arthroplasty, as part of a two-stage exchange procedure. The rationale for the use of spacers is to allow for delivery of local antibiotics, while managing the dead space that is left behind after resection of the components. Spacers also may facilitate subsequent joint exposure during second-stage reimplantation and, depending on their configuration, may improve function during the resection interval. Spacers can be classified as either static or articulating. There are numerous problems that can occur with the use of spacers and relative to the type of spacer used (Table 1).

Knee

In a study by Struelens et al. [1], 57% of patients experienced issues related to the use of articulating spacers in the knee. Of these, 45% were minor problems such as spacer tilting and medio-lateral translation. In their cohort, 12% of spacers had dislocated, fractured or subluxed. Possible reasons for subluxation or dislocation of spacers are inadequate soft-tissue tension and/or incorrect positioning of the spacer. In addition, pre-fabricated articulating spacers typically come in a limited number of sizes and have inadequate morphology offering minimal inherent stability. Articulating spacers rely mainly on soft-tissue tension around the joint for stability and function and soft tissues often have some compromise in this setting.

Soft tissues are not always to blame for instability associated with spacers. Even when proper tension is restored during surgery, later bone loss may cause further motion and subsidence of the spacer, leading to instability and dislocation. A study by Lau et al. [2] reported that sagittal subluxation was associated with bone defects on the tibial side. The same study found that coronal subluxation tended to be correlated with larger bone defects on the femoral side although this finding did not reach statistical significance. Lanting et al. [3] found that subluxed knees, more than one standard deviation from the mean in the sagittal plane, had lower early- to mid-term Knee Society Function Scores, but did not show any significance in other patient-reported scores like Medical Outcomes Study Short Form-12 (SF-12), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Coronal subluxation did not affect any of these scores.

Hip

There are fewer reports related to complications of spacers in the hip. A study by Jung et al. [4] reported a total complication rate with hip spacers of 40.8% (i.e., 17% dislocations, 10.2% fractures of the spacer, 13.6% femoral fractures). These numbers were not confirmed by Faschingbauer et al. [5] who had an overall mechanical complication rate of 19.6 % (i.e., fracture of the spacer 8.7 %, dislocation 8.7 %, femoral fracture 0.7 %, protrusion into the pelvis 0.7 %, dislocation and spacer fracture 0.7 %). According to Faschingbauer et al., 50% of the patients with a spacer fracture remained asymptomatic (the spacer fracture occurred at the stem area of the spacer) and showed a stable condition, while the other half underwent spacer revision. A fracture of the proximal femur occurred in one of the study patients (0.7 %), which was managed operatively. Closed reduction and stable retention was possible in only 4 of 12 dislocations. All other patients with a spacer dislocation underwent a subsequent operation with spacer revision. There was no comparison in these studies between the functional and morbidity outcomes between the revised and the nonrevised spacers with respect to associated complications.

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5.5. TREATMENT: TWO-STAGE EXCHANGE

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QUESTION 1: What is the optimal timing for reimplantation of a two-stage exchange arthroplasty of the hip and knee?

RECOMMENDATION: The optimal timing for reimplantation of a two-stage exchange arthroplasty of the hip or knee has not been established. Reimplantation may be performed when the treating medical team feels that the infection is under control.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 4%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

There is no conclusive evidence for defining the optimal timing between resection arthroplasty and reimplantation in a two-stage revision arthroplasty for periprosthetic joint infections (PJIs). Multiple studies have reported time to reimplantation ranging from a few weeks to several months or even years [1–11]. Literature has utilized various definitions for PJI two-stage treatment success or failure as well as different variables influencing the timing of reimplantation. Due to this heterogeneity, they have failed to answer this

question. Success of treatment with a two-stage arthroplasty varies between <70 to 100%, with no direct correlation to the spacer time interval [1,2,6,7,9,11].

Several studies have reported on time to reimplantation and its influence on success or failure. Haddad et al. reported no increase inreinfection rates by reducing the interval to three weeks [5]. Sabry et al. found that an increased duration between resection and reimplantation was associated with higher rates of infection recurrence in a cohort of 314 infected total knee arthroplasties (TKAs) treated with two-stage exchange [7]. Their median interval between stages was 103 days (range, 2 to 470 days). A study by Kubista et al. [8] also found that a longer time period between spacer insertion and reimplantation was associated with increased PJI recurrence. In contrast, Babis et al. obtained a 100% success rate when using a long interval—mean 9 months (range, 8 to 12 months)—in a group of patients with a high percentage of multiresistant bacteria [9].

One common belief is that a delayed second-stage or reimplantation will result in a higher rate of treatment success. However, this is not based on strong evidence and may lead to an unnecessarily long inter-stage interval with its associated morbidity. Aali-Rezaie et al. [10], in a recent, large retrospective cohort study evaluating patients with two-stage exchange arthroplasty, did not detect a clear association between time to reimplantation and treatment failure. Furthermore, they found that delaying the time to reimplantation did not significantly improve treatment success of two-stage exchange arthroplasty. In addition, Vielgut et al. found, in a study of 76 hip infections, that patients who had their reimplantation between 4 and 11 weeks had a significantly higher success rate when compared to less than 4 and greater than 11 weeks [6].

When deciding on the optimal timing for reimplantation, most surgeons prefer to rely on a combination of clinical evaluations, such as a completely healed wound, no pain and serologic tests trending downwards after a period of antibiotic therapy [11]. Various studies recommend a complete workup with normalized laboratory and clinical variables to assure infection control prior to reimplantation.

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QUESTION 2: Is it safe to retain a stable cement mantle for later use in patients undergoing resection arthroplasty for periprosthetic joint infections (PJIs)?

RECOMMENDATION: Meticulous debridement and removal of all foreign material, including cement, should be part of resection arthroplasty in the management of PJIs. Limited data suggests that under strict conditions and following a meticulous surgical technique, a stable cement mantle in the femur may be left in place for later use in order to minimize damage to the femoral bone stock.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 63%, Disagree: 29%, Abstain: 8% (Super Majority, Weak Consensus)

RATIONALE

Historically, resection arthroplasty for PJIs involved removal of all the foreign material including cement, as these materials can act as a nidus for biofilm and persistence of infection [1–5]. However, removal of the cement mantle increases operative time and causes increased morbidity through bone loss and fractures. The in-cement revision technique is a useful, well-described technique utilized in aseptic conditions to avoid the tedious task of cement removal and therefore avoid complications associated with cement extraction [6–10]. Retention of an intact cement mantle in cases of resection arthroplasty for PJI would be preferable to avoid the morbidity associated with its removal and would make subsequent reimplantation technically easier.

The concern for retaining cement in the setting of PJI has been supported by in vitrostudies. Kendall et al. examined microbial growth of staphylococcal species on the surface of antibiotic-loaded cement discs incubated in broth. While the broth itself was sterilized by the discs after 96 hours, growth was consistently seen on the surface of the cement discs themselves. The cement, therefore, seemed to be a habitable surface for continued growth of bacteria, despite elution of antibiotics [11]. Mariconda et al. demonstrated that fluid around antibiotic-loaded cement that is sonicated can yield positive cultures, even if aspiration fluid was culture-negative, indicating that biofilms can persist on antibiotic-loaded cement [12]. Tunney et al. and Minelli et al. showed that biofilm could form even

on antibiotic-loaded cement, depending on the inoculum and the type and dosing of the antibiotic agent [13,14]. Although Griffinet al. could not demonstrate biofilm formation in explanted spacers, Ma et al. demonstrated that 30.7% of spacers had bacterial contamination at the time of the second stage [15,16]. This laboratory data should give some cause for concern for the retention of cement in the setting of infection, even if loaded with antibiotics.

The clinical data on this topic is extremely limited. There are two case series that examine this specific issue, both involving a stable cement mantle in revision total hip arthroplasty for infection. Morley et al. reviewed 15 total hips with two-stage revisions for PJIs while retaining the original cement mantle and reported infection-free outcomes in 14 of 15 patients [17]. The authors used a very strict selection criteria for the patient cohort. These selection criteria, which included a stable cement mantle, prior use of antibiotic-loaded cement and meticulous burring of the cement mantle in order to remove biofilm and liberate antibiotics were vital to the success of this technique.In a similar study, however, Leijtens et al. reported success in only 2 out of 10 patients undergoing two-stage revision total hip arthroplasty for infection at an average of 26 months [18]. It should be noted that this study did not mention whether the existing cement mantle contained antibiotics or not.

There is only one Level IV study showing good results with a retained stable cement mantle for later use in resection arthroplasty in the treatment of PJIs. While this technique presents theoretical advantages, there is a lack of robust evidence in the literature to support its routine use. Direction for further research might include the use of chemical debridement agents, such as dilute povidone-iodine, chlorhexidine irrigation and/or acetic acid preparations, which some evidence suggests might help eradicating microbes and biofilms in some settings [19]. The role of chemical debridement agents in eliminating sessile bacteria and biofilm on the surface of retained cement has yet to be explored. With further research, the answer to this question might become known.

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QUESTION 3: Should surgeons make an effort to remove cement that has extruded into the pelvis or at difficult anatomical positions in patients with periprosthetic joint infections (PJIs)?

RECOMMENDATION: The orthopaedic surgeon should carefully consider whether the potential benefits of cement extraction from the pelvis or difficult anatomical positions outweigh the potential risks of persistence of infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 85%, Disagree: 9%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Extrusion of cement during primary arthroplasty is reported to occur in 25% of patients [1]. Bacteria can form biofilm on foreign bodies in patients with PJIs [2]. Therefore, in patients with PJIs who are undergoing resection arthroplasty, it is recommended that the prosthesis and all foreign material including bone cement be removed and thorough debridement performed. Whether or not

cement in the pelvis or in difficult anatomic positions contributes to the risk of persistent infection after revision arthroplasty has not been studied.

When cement is extruded into the pelvis or difficult anatomic positions during primary arthroplasty, there is a risk of neurological (obturator nerve palsy [3,4], femoral [5] or sciatic nerve involvement [6]), urological (such as a foreign body in the bladder wall [7]) or vascular (with compression of the external iliac vein [8]) complications. During extraction of extruded cement, the risk of these complications may be even greater due to the manipulation needed for extraction.

It is common wisdom and belief among surgeons that foreign material in an infected joint may harbor biofilm formed by the infecting organism. Leaving behind foreign material during resection arthroplasty and debridement, thus, runs the theoretical risk of allowing for biofilm and infection to persist and could therefore potentially jeopardize the success of surgical debridement. The latter dogma has actually never been proven in a conclusive study. It is also known that removal of foreign material, such as cement, from anatomically sensitive and/or inaccessible areas may require a wider surgical approach (such as laparotomy for extruded cement into the pelvis) or manipulation of structures such as organs (e.g., bladder, bowel), vessels (e.g., vena cava or major veins) or nerves (e.g., sciatic or plexus). The manipulation of these structures may threaten the life of the patient and/or lead to catastrophic complications. Thus, we believe surgeons should exercise their wisdom when dealing with patients with PJIs and extruded cement or other foreign materials in anatomically sensitive and/or inaccessible areas.

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QUESTION 4: Does the use of non-antibiotic-impregnated allograft for bone defects during reimplantation increase the risk of recurrence of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: There is no evidence to demonstrate that using non-antibiotic impregnated allograft for management of bone defects during reimplantation (following PJIs) increases the risk of recurrence of SSIs/PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 88%, Disagree: 9%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Systematic reviews were undertaken using PubMed, Cochrane Library, SCOPUS and Google Scholars databases and relevant papers were reviewed. During review, it became evident that there is a dearth of information directly assessing treatment of PJIs when a non-antibiotic-impregnated allograft was used. Overall, 51 papers were reviewed in full. The evidence is summarized below.

Following the increased popularity of the use of allograft bone in tumor surgery in the 1970s [1], infection has become a major concern. The early reports of infection rates range from 13.2% by Mankin et al. [2] to 11.7% by Lord et al. [3] and were followed by 7.9% in a comprehensive report by Mankin et al. in 2005 [4]. All authors believed that higher rates of infection could be attributed to the disease nature, extent, duration and complexity of the procedures and not related to the allograft itself [2–4].

Tomford et al., in a retrospective study, reviewed 324 patients who received allografts and showed a negligible clinical incidence of infection. The incidence related to the use of large allografts was approximately 5% in bone tumor and 4% in revision of a hip arthroplasty [5]. These rates of infection were not substantially different from those that have been reported in similar series in which sterilized prosthetic devices were used [6]. One of the early reports of allografts in revision total hip arthroplasty (THA) was published by Berry et al. [6]. They used bone allografts in 18 patients during two-stage revision of septic THA failures. At a mean of 4.2 years after reimplantation, only two patients had a recurrence of the infection (11%).

Several retrospective cohort studies have evaluated the use of allograft bone during total hip reimplantation surgery, the second-stage of planned two-stage exchange arthroplasty for infection. The majority of these studies have demonstrated recurrent infection rates of 0 - 9% in cohorts consisting of 11 -27 patients with mid- to long-term follow-up [6-12]. Two studies reported less favorable reinfection rates of 11% (18 patients, mean 4.2-year follow-up) and 14% (57 patients, mean 9-year follow-up) [13,14]. Traore et al. reported a higher rate of 20% for reinfection at mean 3 years [13]. Loty et al. reported a cohort of 90 cases with 8 (9%) reinfections over an unknown follow-up period in one-stage hip revision for infection [14].

Lange et al. performed a systematic review on using bulk allograft for second-stage re-implantation of hip arthroplasty and revealed a reinfection rate of 4 out of 43 (9.3%) at a average follow-up of 6 years. This was comparable to the reinfection rate reported for two-stage revision without using allograft [15]. Alexeeff et al. also had no recurrence of infection in 11 septic failures of THA that underwent two-stage revision THA using massive structural allografts and were followed for an average of 47.8 months [10].

Tsahakis et al. reported on 15 cases that used allograft for revision knee surgery, and of the three infected knees in their case series, there was no recurrence of infection [16]. Wilde et al. performed a retrospective review of 16 revisions total knee arthroplasties (TKAs) with allograft. There were two infected cases and neither of these experienced reinfection [17]. Stockley et al. reviewed 32 deep-frozen irradiated allografts used for the reconstruction of bone defects in 20 knees with an average follow-up of 4.2 years. Three knees developed infection (9.3%) and one of these was a revision for infection. However, they did not believe that the allograft was the source of sepsis [18].

Further reports by Harris et al. [19] (14 patients including 2 infected cases), Mow et al. [20] (15 structural allografts) and Engh et al. [21] (35 allografts) examined revision TKA cases and found no cases of reinfection [19–21]. Ghazavi et al. reported three infections (7%) using bulk allograft in 38 patients, including three infections that underwent revision. Two of the three cases who had previous infections experienced reinfection [22]. In a report by Clatworthy et al. on 52 cases, there were six infections, all of which underwent revision TKA with a bulk allograft. One of the six patients who had a previous infection developed recurrence of infection [23].

English et al. reported their results of using impaction allografting in the second stage re-implantation of 53 infected hip arthroplasties. After a mean follow-up of 53 months, four patients had recurrence of infection (7.5%) [24]. In reports by Dennis et al. (32 allografts) and Garino et al. (eight cases of impaction allografts), there were no infections at final follow-up [25,26].

Hockman et al. reviewed 65 consecutive revision TKAs including 12 infections at a minimum 5-year follow-up. Three of the 12 (25%) previously infected cases developed infections. They concluded that knees originally revised for infection were more likely to fail [27].

Bush et al. reviewed options for reconstructing massive bone loss and recommended against using allograft in some situations, including chronic infections [28]. Backstein et al. reported 68 cases of massive allografts for revision TKA and 11 of these were septic revisions. They found four infections (6.5%). The authors did not include how many of them had surgery for septic revisions. They believed that, because of the large size of the utilized allograft bone and the number of previous surgeries the patients had, the infection rate was modest [29].

Lotke et al. reported on 48 cases including one infection that received impaction allografting in revision TKA. At an average follow-up of 3.8 years, they had two infections (5%) [30]. Bezwada et al. reviewed 11 knees in 10 patients who underwent revision with distal femoral allografts and stemmed components. After a mean follow-up of 42 months they had no infections. They recommended against the use of plate fixation to decrease extensive soft tissue dissection and the risk of infection [31].

Engh et al. reported no cases of reinfection in 49 revision knees with severe tibial bone defects, five of which were revisions for infection [32]. Rudelli et al. reported on 32 loose and infected total hip arthroplasties that underwent revision with a bone graft in a one-stage procedure. After a mean follow-up of 103 months, infection recurred in two (6.2%) cases [33].

Burnett et al. reported on 28 knees that underwent revision TKA with an allograft at a follow-up of 48 months. Only one patient (3.5%), who received a cancellous graft for a contained defect, developed an infection. They did not mention if this was an infected revision [34]. Lyall et al. investigated 15 revision TKA patients, including three revisions for infections with severe tibial bone loss. These patients were followed for a mean of 5.4 years and they found one (6%) recurrence of infection at 3.5 years [35].

Bauman et al. retrospectively reviewed 74 patients (79 knees) who had revision TKAs with structural allografts. Of this cohort, 65 patients (70 knees) were followed for a minimum of 5 years or until revision or death. Five of sixteen failures were secondary to infection (7.1%). Two of these patients had a history of infection and two had local wound problems at the time of revision surgery requiring muscle flap or skin grafting. The authors concluded that the large bulk allografts were more likely to fail secondary to infection or nonunion [36].

In an overview on management of bone loss in revision TKA, Lombardi et al. did not mention infection as a disadvantage (i.e., late resorption, fracture, nonunion, or risk of disease transmission) of using an allograft [37]. Lee et al. retrospectively reviewed 27 patients who underwent two-stage revision arthroplasty using structural allografts to treat massive bone defects in infected hip arthroplasty. After a mean follow-up of 8.2 years, only one patient (3.7%) experienced a reinfection [12].

Richards et al. reported on a cohort of 24 patients reconstructed with femoral head allografts at the time of revision TKA and they compared them to 48 cases without allograft. All reported quality of life scores were higher in the allograft group. They did not observe any failures [38]. Wang et al. reported 28 patients with femoral head allografts for revision TKA at a mean follow-up of 76 months. They had no complications and no infections [39]. Vasso et al. reviewed multiple papers on options for management of bone loss in revision TKA. They concluded that modular metal and tantalum augmentation may considerably shorten operative times with a potential decrease in the incidence of complications, including infection, associated with the use of allografts [40]. In a review of 27 patients who had undergone revision TKA using a fresh frozen femoral head allograft and followed for 107 months, there was one (3.7%) recurrence of infection [41].

Recently, Beckmann et al. performed a systematic review on the treatment of revision TKA with bony structural allografts (overall including 476 cases) and porous metal cones (overall including 223 cases). They compared the failure rates using a regression model with adjustment for discrepancies in follow-up time and number of grafts used (femoral, tibial, or both). They did not separate septic revisions from aseptic revisions, but there was little difference in the infection rates between allograft and porous metal groups [42].

Mancuso et al. also reviewed the available English literature since 2007 on options for reconstruction of bone defects in revision TKA. Infection was reported in 8 of 271 (3%) allografts, 43 of 662 (6%) metal cones and 27 of 901 (3%) sleeves, indicating that the use of allografts did not lead to a higher rate of infection than metal cones or sleeves [43].

Sandiford et al. compared femoral head structural allografts and trabecular metal cones for the management of severe bone defects during revision TKA. They evaluated 30 allografts and 15 metal cones at a mean follow-up of nine years and found no differences in pain, function, or repeat revision. The reason for revision was infection in two patients. They observed no reinfection in either group, although one patient in the allograft group devel-

oped a periprosthetic fracture and developed an infection after treatment of this fracture [44].

Infection is the major cause of failure in revision TKA (44.1%) [32] and the risk is even higher in patients with septic revisions [45]. However, given the absence of any prospective controlled studies, the paucity of comparative studies with control groups and the conflicting data in case series,we could not reach any conclusion regarding the effect of using an allograft on the rate of infection in revision arthroplasty for septic failures.

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5.6. TREATMENT: SURGICAL TECHNIQUE

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QUESTION 1: Does arthroscopic surgery have any role in the treatment of acute or chronic periprosthetic joint infection (PJI) of the knee or the hip?

RECOMMENDATION: Arthroscopic surgery has no role in the treatment of acute or chronic PJI of the knee or hip.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 6%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Principles of managing PJIs include removal of infected soft tissue, bone and biofilm containing implants. Advocates of debridement and implant retention, typically for acute infection, rely on sensitive antibiotics to the causative organism and its biofilm. In open debridement, antibiotic and implant retention (DAIR), modular components are typically exchanged to improve access for thorough debridement and to reduce the biofilm volume.

Although arthroscopic surgery is attractive as a less invasive procedure than open debridement for the treatment of PJIs, it can be technically challenging to access all compartments of the joint to perform a proper debridement, risking partial surgical treatment. Partial surgical treatment risks failure to eradicate infection, side-effects from long-term antibiotic use and possible emergence of antibiotic resistance. Outcomes of staged-revision following failed partial surgical treatment are worse [1,2]. The evidence for arthroscopic washout and debridement is predominantly small, non-comparative studies [3–10]. Comparative studies of DAIR comment that successful control of infection was lower if managed arthroscopically [1].

Success is typically viewed as long-term eradication of infection off antibiotics, but function must be maintained. Poor function can be caused by infection or from pain due to loose components, inflamed soft tissues and wound-management issues caused by sinus tract formation. Aggressive surgical management involving the excision of bone, soft tissue restraints and removing well-fixed implants can challenge functional outcomes. Each individual PJI requires consideration of surgical aggressiveness to eradicate infection relative to maintaining function.

Arthroscopy in Total Knee Arthroplasty (TKA) PJI

Arthroscopic treatment of TKA PJI has variable success from 38-100%. Flood and Kolarik were the first to describe successful arthroscopic treatment of two patients with a late acutely infected TKA [3]. Waldman et al. reported that 6 of 16 patients (38%) with infected TKA who presented with less than 7 days of symptoms and who were treated with arthroscopic surgery retained their prostheses at a mean follow-up of 64 months [4]. Dixonet al. reported that 9 of 15 patients (60%) with late acute infections of TKA retained their prostheses after a mean follow-up of 50 months [5]. Chung et al. reported that 10 of 16 patients (62.5%) with late acutely infected TKA who were treated with arthroscopic surgery within 72 hours of onset of symptoms retained their prostheses at a mean follow-up of 47 months [6]. The six patients who failed arthroscopic debridement underwent successful infection eradication with open debridement with polyethylene insert exchange.

Ilahi et al. reported 5 patients with late acute TKA infections who were treated with arthroscopic surgery within 7 days of symptom onset; all patients retained their prostheses after a mean follow-up interval of 41 months [8]. Liu et al. reported on 17 patients who had late TKA infections who were treated with arthroscopic debridement combined with a close continuous irrigation-suction system; at a mean follow-up 27.5 months, 15 (88%) retained their prostheses [7].

Byren et al. [11] compared arthroscopic treament with open debridement in a retrospective review of 112 cases, 51 of which were of hips and 52 of which were of knees, to assess outcomes of patients treated for PJIs. The group found that the 15 patients with PJIs who were treated with arthroscopic washout had a significantly lower rate of success (47%) than the 97 treated with open debridement (88%) (hazard ration (HR) = 4.2, 95% confidence interval (CI), 1.5–12.5, p = 0.008). Compared to the other series, the majority of the organisms were staphylococci and 77% were early postoperative within 90 days of the implantation.

Combining these papers results in 86 infected primary TKA treated with arthroscopic debridement. In total, 54 patients (63%) were successfully treated. The success rate was affected by the infecting organism which was available in only 71 cases. The organism results were: Streptococcus 12/14 (86%), *Staphylococcus epidermidis* 11/16 (69%), *Staphylococcus aureus* 14/26 (54%), gram-negative bacilli 3/6 (50%), Mycoplasma 1/2 (50%), no growth 5/6 (83%) and polymicrobial 0/1 (0%).

The time between implantation and infection was described in 60 patients. There were eight (13%) postoperative infections using six weeks as a cut-off. Arthroscopic washout and debridement was successful in four (50%) cases. The remaining 52 cases were described as late-acute PJI with success in 36 (69%) cases.

Arthroscopy in Total Hip Arthroplasty (THA) PJI

Only two studies investigated arthroscopy in THA PJIs [9,10].In a prospective study, Hyman et al. reported eight consecutive patients who had late acute PJIs after primary THA andwere treated with arthroscopic surgery [10]. Seven infections were caused by Streptococci and one by coagulase-negative Staphylococcus. After a mean follow-up of 70 months (range, 29-104 months), there were no recurrent infections. The authors concluded that arthroscopic irrigation and debridement could benefit well-selected patients with late-acute periprosthetic hip infections.

Another study included two patients with infected THA who were successfully treated with arthroscopic debridement followed by intravenous therapy; the report did not provide additional details [9].

Arthroscopy in Chronic Late Infections

The inclusion criteria for most of the studies mention a short duration between the presentation of symptoms and time of

arthroscopic debridement and therefore there is no clear evidence exploring the role of arthroscopy in chronic late infections. The 112 PJI series treated by DAIR included 35% that were over 90 days from onset of symptoms to debridement, but this was a mixed series of predominantly open debridement with only 15 performed arthroscopically [11]. There was no sub-group analysis of the arthroscopic group available to make conclusions regarding timing or utility in treating chroniclate infections.

There is a practical role of arthroscopy as part of the management of PJIs in chronic-late infections. Arthroscopy can be part of the diagnostic workup of a painful arthroplasty allowing dynamic inspection of the components for instability and wear, ruling out non-infective causes, visualization of the synovium and obtaining multiple samples for microbiology and histology. In patients who are not well due to sepsis, particularly where delaying surgery while waiting for appropriate equipment or surgical expertise risks further health deterioration, arthroscopically obtaining microbiological samples prior to commencing antibiotics and joint washout to reduce the bacterial load can allow time for appropriate preoperative planning for definitive surgical management of the PJI.

In conclusion, the studies describing arthroscopic management of PJIs generally analyze few patients and have very specific inclusion criteria, making the data difficult to generalize. Combining the available studies, the success from acute late infection is approximately 60%. The only comparative series available concluded that arthroscopic debridement has a significantly lower success rate than open debridement. Future work could investigate specific bacterial infections that lack an ability to form a biofilm and are sensitive to long-term oral antibiotics that may be susceptible to more conservative surgical management. Overall, based on the current literature, we recommend against the routine use of arthroscopic surgery for the management of PJIs.

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QUESTION 2: Do all metallic implants need to be removed to eradicate periprosthetic joint infections (PJIs)? Does this apply to other metal hardware present (e.g., hook plates, cables) as well?

RECOMMENDATION: Complete debridement of the hip or knee joint and removal of all hardware is ideal during surgical treatment of PJIs. This principle should be followed whenever possible. However, there may be rare cases of PJIs when removal of all hardware may lead to marked morbidity and preclude future reconstruction. In the latter situation, some hardware may be retained.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 97%, Disagree: 3%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The treatment of PJIs involves the surgical removal of infected tissue and hardware in order to decrease the potential infectious bioburden. Many infecting organisms are capable of forming biofilms on foreign material surfaces. Therefore, all foreign material, including bone cement and hardware, should be removed to better treat or control PJIs.

Retained hardware prior to total knee arthroplasty (TKA) is a known risk factor for PJIs. In vitro studies demonstrate the ability of bacterial biofilms to adhere to orthopaedic implants [1–3], and the presence of extravascular foreign bodies in animal models increases the threshold for infection 100,000-fold due to a hypothesized granulocyte defect around implants [4,5]. Manrique et al. demonstrated a trend toward increasing rates of PJIs with partial or complete retention of hardware, but there was no statistical significance when compared to controls [6]. There are limited reports highlighting the need to remove hardware from around the hip or knee in the setting of PJIs. Suzuki et al. reported on their institutional experience of 2,022 TKAs. Seventeen infections were identified with a prior history of an open reduction internal fixation and the presence of retained internal fixation material was correlated with postoperative infections [7]. However, the mere presence of prior fixation material cannot fully be separated from the increased risk of PJIs in a multiply-operated joint.

While the removal of all implant materials is thought to provide the greatest benefit, the degree of tissue or implant excision necessary for infection control is currently unknown. The inability to control infection in the setting of retained hardware is often thought to be due to residual bacteria. In many cases, the morbidity of removing implants or other hardware is considered too great, and, therefore, implants are retained. Evidence for this is supported in the practice of debridement with retention of components. Partial radical debridement has proven successful in a small case series where 17 of 19 patients remained infection free with retained cemented or uncemented femoral prostheses [8,9]. In addition to the retention of metal components, there are mixed results when considering cement retention. McDonald et al. reported that 3 of 7 patients with retained polymethyl methacrylate cement had a recurrence of infection, whereas only 8 of 75 patients in which the cement had been completely removed had recurrence of an infection ($p < 0.01$) [10]. There is evidence, however, that retaining cement that would otherwise be deleterious to remove is safe and effective in the setting of infection [11].

The retention of plates, hooks or cables will often occur in the periprosthetic fracture setting. Evidence exists for successful fracture union with retained hardware in the setting of infection [12–14]. Berkes et al. demonstrated that 71% (86 of 121) successful fracture unions with operative debridement, retention of hardware and culture-specific antibiotics and suppression [12]. The retention of an intramedullary device, however, was associated with higher failure rates ($p< 0.01$). Rightmire et al. demonstrated a 68% (47 of 69 cases) success rate for hardware retention and debridement in the treatment of infected fractures [13]. When considering these results, it is important to note the clinical differences between infected fractures and infected periprosthetic fractures that communicate with the joint space, which is typically a large effective space. In postoperative spine infections, Picada et al. reported on 24 of 26 fusions healing without removal of hardware, although they achieved these results most often with secondary closure [15].

When retaining components, rifampin should be considered as part of the antibiotic regimen, particularly for staphylococcus infections. Zimmerli et al. conducted a randomized, placebo-controlled, double-blind trial and demonstrated a 12 of 12 (100%) infection control rate in the ciprofloxacin-rifampin group compared to the ciprofloxacin-placebo group (7 of 12 - 58%) when implants were retained [5]. Additionally, Trebse et al. demonstrated improved success rates with the addition of rifampin [9].

The removal of all infected material, organic or inorganic, improves the ability to control PJIs by reducing bacterial bioburden and helping to eliminate biofilm. However, the removal of these materials must be balanced with the morbidity of their removal and considered carefully in surgical planning.

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QUESTION 3: Should all knee compartments be resected during resection of an infected unicondylar knee arthroplasty (UKA)?

RECOMMENDATION: Yes, during resection of an infected UKA, other compartments of the knee, including the fat pad, should also be resected.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 80%, Disagree: 14%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

UKA has become increasingly popular among those affected by single-compartment osteoarthritis in that it preserves the integrity of the remaining knee compartments and ligaments, permitting the operated knee to be functionally and kinematically similar to the

natural knee [1]. Similar to total knee arthroplasty (TKA), periprosthetic joint infections (PJIs) after UKAs can occur with reported rates ranging from 0.2 to 3% [2,3].

There is surprisingly minimal literature regarding the treatment and outcomes of PJIs after UKA. For chronic PJIs, Labruyère et al. demonstrated 100% survivorship in a series of nine infected UKAs treated with one-stage exchange arthroplasty to a TKA at a median of 60 months, five of which were initially unsuccessfully treated with synovectomy, joint lavage and antibiotics [2]. The authors also noted that wedges (n = 6) and stems (n = 5) were required in the majority of patients. Bohm et al. performed exchange arthroplasty in two cases of PJI with one resulting in a femoral amputation [4]. One study revised two cases via a second, single-stage UKA in conjunction with synovectomy and prolonged antibiotic therapy, with the new implants being the same size as the initial implant, and with one implant being cemented with antibiotic cement, while the other case did not have a cemented implant [5]. Four studies revised nine knees to a TKA [6–9], with one study having two re-revisions following initial resection for recurrent infection [9]. Furthermore, Hamilton et al. performed three two-stage exchange arthroplasties, with one initially undergoing irrigation and debridement but ultimately requiring revision to a TKA via a two-stage exchange arthroplasty for recurrent infection [10].

Three studies successfully treated deep infection following UKA with retention of the implant with the first reporting one case treated with debridement and inlay exchange [8], the second reporting two cases treated with washout, debridement and bearing/liner change [9] and the third reporting one case treated with synovectomy and placement of gentamicin chains [11].

It is clear through the current literature that there are several viable options to treat infections following UKAs. The method that the surgeon chooses to use should be selected based on the severity and chronicity of infection as well as the amount of remaining native bone and cartilage. Bone loss is also not uncommon in the setting of infection [5]. In acute infection and in the absence of involvement of other compartments, debridement and retention may be a reasonable option. In patients with bone loss, chronic infections, or with infections that may be difficult to eradicate due to a resistant or challenging organism, a one-stage exchange or two-stage exchange arthroplasty to a UKA or TKA may be performed with the inclusion of a wedge or stem as indicated. If two-stage exchange arthroplasty is being performed, during resection arthroplasty other compartments and the fat pad should also be resected as they may harbor bacteria. This practice also allows for insertion of a proper spacer.

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QUESTION 4: Can sub-radical resection arthroplasty (leaving parts of implants in place) be considered during management of patients with chronic periprosthetic joint infections (PJIs)?

RECOMMENDATION: Sub-radical resection arthroplasty (leaving parts of implants in place) may be considered during management of patients with chronic PJIs when a component is proven to be well-fixed and its removal precludes opportunity for future reconstruction.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 68%, Disagree: 29%, Abstain: 3% (Super Majority, Weak Consensus)

RATIONALE

Two-stage revision with removal of all prostheses followed by reimplantation has been considered the gold standard to treat chronic PJIs [1–3]. However, the removal process might necessitate the use of additional procedures such as an extended trochanteric osteotomy to perform the removal of a well-fixed stem [4]. This can result in severe compromise of the proximal femur and jeopardize future fixation of a reimplanted stem. Retaining a well-fixed stem or acetabular component can be an option to avoid this in the setting of PJI treatment.

Struhl et al. [5] initially described this technique in 1989. In his case study, a 47-year-old man with a *Staphylococcus epidermidis* infection was treated by removal of the bipolar head, irrigation and debridement, retention of the femoral component and placement of antibiotic-impregnated beads. After seven weeks of intravenous antibiotic therapy, the patient underwent reimplantation of the acetabular component with an uncemented device. At 18-month follow-up, the patient had fully recovered without evidence of

infection. In 2013, Lee et al. [6] reported the results of 17 two-stage reconstructions retaining well-fixed cementless femoral stems in the treatment of PJI. At 2- to 8-year follow-up, 15 patients (88%) had no recurrence of infection and had satisfactory radiological and clinical outcomes. More recently, Ekpo et al. [7] reported on 19 patients with chronic infection whose femoral component was considered to be well-fixed and its removal would result in a marked femoral bone loss. Only two patients (11%), who additionally had failed a prior two-stage exchange, failed their secondary procedure due to recurrence of infection at a minimum of 2-year follow-up. Similar results have been published by Lombardi et al. [7] who had a series of 19 patients. At a mean follow-up of 4 years, 89% were considered to be infection-free. Two more recent publications have looked at results of this procedure with longer follow-up periods [8,9]. In a study by El-Husseiny et al. [8], 18 patients who had partial component retention were evaluated. These were carefully selected cases out of all the 293 patients who were surgically treated for PJIs at their institution. The selection criteria and indications for this approach were those who had complex total hip arthroplasties with ingrown femoral stems or complex acetabular components that were well-fixed [8]. Their reported success rate was 83%. Also, Ji et al. [9] retrospectively analyzed 31 patients. In his series patients underwent retention of components in what they called partial single-stage revision. Either the acetabular or femoral component was retained given that there was evidence of good fixation. Of the 31 patients, 27 were considered to have a good outcome (87.1%) at latest follow-up.

Results of sub-radical resection arthroplasty have shown acceptable success rates ranging from 87-89%. These can be compared to published results of two-stage results, although there is a high variability of reported success rates [10-12]. Only one study reports on one-stage sub-radical resection and retention of well-fixed components with also promising success rates of 87% [9]. We consider that a careful selection of patients with adequate evaluation of fixation is the key to determine if retention of components is a viable option. Although there is a lack of strong evidence, a partial exchange may present a better alternative than complete resection performed in two-stage revision of chronic PJIs when the stem is well-fixed with bone-ingrown stability. We therefore support the use of partial exchange in the treatment of chronic PJIs in selected cases.

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QUESTION 5: Is it possible to have an isolated infection of only a portion of the joint (for example the femur and not the acetabulum, or tibia and not the femur)?

RECOMMENDATION: Unknown. Infection of a prosthetic joint is likely to involve biofilm formation on surfaces of all foreign material. However, there may be rare circumstances when infective organisms may not be able to reach the surface of a well-fixed implant and form a biofilm.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 75%, Disagree: 19%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Using a standardized study search protocol, we performed a comprehensive review and analysis of the literature related to this subject matter. There were no specific studies examining the issue of partial infection of an implant. As a proxy, we examined the literature related to the outcome of surgical treatment of chronic periprosthetic joint infections (PJIs) when partial retention of an implant was deemed appropriate. The primary outcome measure was success of treatment at a minimum of two years, defined as infection-free retention of the implant. The search strategy and inclusion criteria were chronic PJI, total hip arthroplasty (THA), total knee arthroplasty (TKA) and partial retention. Subsequently, our search strategy yielded 9 articles for analysis, including 130 revisions (Table 1). The follow-up period was 2-8 years (mean 4.1 years) or less if failure occurred. We also recorded the types of bacteria and the success rates reported in each study.

There were no studies related to partial retention of TKA components. The overall success rates of eradication of infection ranged from 80-100% (mean 90%). There were 113 acetabulum-only revisions

TABLE 1.List of publications

Author	Year	Journal	Study Period	Country	Population Size
Faroug [1]	2009	Hip International	2004-2009	United Kingdom	2
Anagnostakos [2]	2010	Hip International	1999-2008	Germany	12
Lee [3]	2013	Acta Orthopaedica	2005-2010	South Korea	19
Ekpo[4]	2013	Clin Orthop.	2000-2011	USA	19
Lombardi [5]	2014	Bone and Joint	2011-	USA	7
Fukui [6]	2015	Journal of Orthopaedics	2009-2014	Japan	5
El-Husseiny [7]	2016	Clin Orthop.	2000-2010	United Kingdom	18
Ji [8]	2016	International Orthopaedics	2000-2013	China	31
Chen [9]	2017	International Orthopaedics	2004-2013	China	16

and 17 femur-only revisions. There were 11 failures in the acetabulum-only group (9.7%) and 2 failures in the femur-only group (11.7%). There was no statistically significant difference between the groups. The offending bacteria in the studies are similar to what is expected to be seen in PJIs.

In conclusion, given that in THA and TKA the surfaces of prosthetic material are in contact with bone and knowing the fact that infective organisms are capable of attaching to foreign material surfaces and forming biofilms, we are inclined to believe that partial infection of a prosthesis does not exist. Infective organisms are capable of accessing the effective joint space in the hip and the knee and infecting the entire prosthesis. However, there may be rare circumstances when an implant is well-fixed, either by cement or through osseointegration, and the infective agents are not able to access the prosthesis-bone interface. There were no studies to prove or disprove this assumption. If such a situation existed, then a resolute approach for radical resection of all implants could plausibly lead to an overtreatment and unnecessary morbidity.

Based on the scant data available, it appears that partial retention of well-fixed implants in patients with reconstructive challenges may be a viable option. Such surgical options should only be reserved for patients in whom removal of well-fixed implants are likely to compromise or prevent a later reconstruction. The basic principles of aggressive soft-tissue debridement and complete removal of infected implants should still be obeyed for the majority of patients.

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QUESTION 6: Should heterotopic ossification (HO) be removed during resection arthroplasty of an infected prosthetic joint?

RECOMMENDATION: We recommend that surgeons give strong consideration to removal of accessible HO in an infected prosthetic joint that will not compromise future reconstruction.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 80%, Disagree: 10%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

HO is the presence of bone in soft tissue where bone does not exist. Several risk factors have been associated with HO such as spinal cord injury, head injury, neurologic disorders, osteoarthritis, male gender, burns, other trauma with severe soft tissue damage and joint arthroplasty. The presence of HO at an infected prosthetic joint may be encountered during the time of resection arthroplasty. HO should be removed if present within the infected area, if it interferes with adequate exposure and debridement or when it could potentially interfere with function after resection arthroplasty. Following surgical resection of the heterotopic bone, beneficial effects on the range of motion and pain relief have been described. However, there are still controversies about the optimal timing for surgical resection.

A perioperative regimen is crucial for recurrent prophylaxis. Non-steroidal anti-inflammatory medications (NSAIDs) and radiotherapy have demonstrated beneficial effects on HO prophylaxis with low recurrence rates for a number of indications such as total hip arthroplasty and acetabular surgery. Resection arthroplasty is an effective modality to treat hip arthroplasty infections with HO. If subsequently the patient develops HO while he or she is mobilized, it may facilitate walking on that hip [1].

However, in an extensive search of the English literature we were unable to find any relevant studies that investigate the effect of resection of HO at the time of resection arthroplasty on surgical outcomes.

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QUESTION 7: When soft tissue coverage requires a reconstructive flap, can it be performed at the time of explant or should it be deferred until reimplantation?

RECOMMENDATION: When a soft tissue defect requires a reconstructive flap, it is safe to perform flap coverage at the time of explant or at the time of reimplantation. Early flap coverage at the time of explantation improves soft tissue biology for eradication of infection and allows for earlier mobilization following reimplantation given greater flap maturity.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 95%, Disagree: 2%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

No prospective comparative studies were identified which compared patient groups who have had soft tissue reconstruction flaps performed at the time of explant versus at the time of reimplantation. Much of the literature pertinent to this question comprises heterogeneous series of patients who have exposed or infected total knee arthroplasty (TKA) implants. For TKA soft tissue defects, medial gastrocnemius rotational flaps were most commonly reported. However, many additional rotational and free flaps have been described: lateral gastrocnemius, latissimus dorsi, local fascio-cutaneous, quadriceps advancement, sartorius and rectus abdominus.

Tetreault et al. [1] published the only study identified which evaluated patients based on the timing of flap coverage. Treatment was based on surgeon opinion of insufficient soft tissues. The cohort was heterogeneous, including patients who received medial gastrocnemius flaps at the time of explantation, repeat spacer, reimplantation or irrigation and debridement with liner exchange. There was a non-significant trend toward higher failure rates when the flap was performed with spacer implantation (first or repeat) compared to definitive implants (reimplantation or retention with liner exchange). The overall reinfection rate among all groups was 52% at 4 years. Selection bias likely impacted these results and the authors clearly state that flap timing was based on necessity, rather than a belief that the timing was advantageous. Corten et al. [2] and Young et al. [3] described standardized staged protocols for the management of infected or exposed TKA implants, including soft tissue coverage at the time of explantation, with disparate results. While Corten reports 92% flap survival and one case of reinfection, patients in Young's series had a 29% amputation rate. Ries et al. [4] described a mixed cohort, which included seven patients who underwent soft tissue coverage at the time of spacer insertion. Four patients were treated successfully, while one flap failed and two went on to experience recurrent infection. Gerwin et al. [5] and Browne et al. [6] used flaps between revision stages and at the time of repeat spacer, respectively. Both series reported relative success, with 83% and 78% successful reimplantations, respectively.

McPherson et al. [7] reported on the only identified cohort of staged revision with flap during reimplantation. They described 5% recurrent infections and 33% wound complications among 21 patients.

Based on these published reports, there is limited evidence to support soft tissue flap reconstruction at the time of implant removal and antibiotic cement spacer insertion. By contrast, a small body of literature appears to support deferral of soft tissue coverage until reimplantation of a revision implant. However, these patient populations are not necessarily comparable within the limited body of evidence available. Most studies report high rates of complications, including recurrent infection, recurrent soft tissue defects and subsequent limb loss, highlighting the difficulty of this clinical problem regardless of treatment approach. Based on this literature, as well as experience, we prefer the former approach, given the benefits of improved soft tissue coverage and biology to the eradication of infection. Furthermore, performance of flap coverage at the time of explantation allows for unrestricted rehabilitation following later reimplantation.

Of note, numerous older studies were identified which describe the usage of soft tissue flaps to facilitate implant retention; however,

this approach is not considered consistent with modern, evidence-based management of exposed, infected arthroplasty implants.

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5.7. TREATMENT: PROSTHESIS FACTORS

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QUESTION 1: Does the use of cemented or cementless components at the time of reimplantation affect the success of treating chronic periprosthetic joint infections (PJIs)? If yes, what is the optimal antibiotic(s), dosage and cement to maximize antibiotic delivery and mechanical properties of the cement?

RECOMMENDATION: There is no evidence to suggest that the use of cemented or cementless components at the time of reimplantation affects the success rate of infection treatment. However, the mode of fixation may affect implant survivorship. The bone mass and the quality should dictate the choice of implant and the mode of fixation during reimplantation. If cemented prostheses are used, consideration should be given to the addition of antibiotics directed towards the infective organisms at the time of reimplantation.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 93%, Disagree: 4%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Currently, both one-stage and two-stage revisions for the treatment of hip and knee PJIs have been reported with good results [1]. Regardless of the approach utilized, the optimal method of implant fixation (cemented versus cementless) for PJI treatment success at the time of reimplantation remains unclear. When dealing with septic revisions, the surgeon is faced with two goals: infection eradication and achieving durable fixation [2]. Cement fixation has many advantages including immediate fixation regardless of bone quality, the ability to impregnate with antibiotics/antifungals and the ability to secure impaction graft or large bulk allografts [2]. The disadvantages include sclerotic or limited periarticular bone necessitating longer stems with cementation into virgin cancellous bone further from the joint in question. In the event of reinfection, removal would be technically difficult with high morbidity. The advantages of cementless fixation include the benefit of long-term biologic fixation, ease of removal in the event of acute reinfection with lower morbidity and modularity to separately address implant fixation as well as restoration of biomechanics [2]. The overall survivorship of implants in revision surgery (aseptic and septic) has historically favored cementless fixation [3-8].

However, the literature does not support one method of fixation over another with regard to infection cure rate. Furthermore, there is no data to guide choice or dose of antibiotic to be used in the cement during reimplantation. The body of literature on fixation technique used at the time of reimplantation in two-stage procedures consists of very-low quality, small, single-center retrospective studies with only half providing adequate descriptions of the reimplantation procedure and/or whether cement was used (Table 1). The definitions for successful outcomes, antibiotic management postoperatively, adjunct antibiotic delivery devices (beads, allograft, etc.) and other aspects of surgical management were heterogeneous across different studies. Similar heterogeneous data has been reported for one-stage revision as summarized in a recent systemic review by George et al. [9]. To date, there has not been a randomized controlled trial to answer this question. Overall, cementless hips appear to be the most common approach during reimplantation with good clinical outcomes (83 - 95% successful outcomes). By contrast, when described, knee reimplantation with cemented components is common with comparable outcomes (76 - 93%, Table 1), but cementless or hybrid fixation is gaining popularity [8].

Few studies have specifically investigated the presence or absence of cement use with infection cure rates. Chen et al. explored risk factors for clinical failure following two-stage total hip arthroplasty (THA) revision for infection and a multivariate analysis did not demonstrate that cementation was associated with outcomes [10]. Sánchez-Sotelo et al. retrospectively reviewed 169 hips with infected arthroplasty, all of whom had two-stage reimplantation for the treatment of an infected THA [11]. In the second stage, the femoral component was fixed with antibiotic-loaded bone cement in 121 hips; the remaining femoral components and all acetabular components were cementless. The method of femoral component fixation, either with or without cement, did not correlate with risk of

TABLE 1. Descriptive observational studies of outcomes following two-stage revision for periprosthetic joint infections (PJIs)

Author, Year	Total Cases of Two-stage Revision	Hip or Knee	Cemented or Cementless	Cure Rates
Barrack [13] 2002	12	Hip	Not described	100%
Dieckmann [14] 2014	43	Hip	Cementless	93%
Durbhakula [15] 2004	20	Hip	Not described	90%
Etienne [16] 2003	32	Hip	Not described	~90%
Chen [10] 2015	157	Hip	Cementless /hybrid/full cementation 122 (78%)/31 (20%)/4 (2%)	91.7%
Koo [17] 2001	22	Hip	Cementless	95%
Hsieh [18] 2004	122	Hip	Acetabulum 107/119, Femur 68/107 were cementless	95%
Fink [19] 2009	36	Hip	Cementless	100%
Houdek [20] 2015	57	Hip	Cementless	84%
Berend [21] 2013	189	Hip	Cementless	83%
Toulson [22] 2009	84	Hip	Hybrid 44%, cementless 43%, cemented 13%. "If a cemented prosthesis is implanted, antibiotic cement is used. The standard doses for antibiotics in implant cement are 1.2 gm of tobramycin per packet of cement, and 500 mg of vancomycin per packet of cement." Failures evenly split 3/3	95%
Fehring[2] 1999	25	Hip	Cementless."Our criteria for using cement for reimplantation are similar to those in standard revision cases. If the bone quality is such that stable fixation and bone ingrowth are unlikely, a cemented construct is recommended."	92%
Romano [23] 2012	183	Hip	Cementless. In a case-control study, outcomes are the same as per aseptic revisions (Romano 2010).	94.6%
Cabo [24] 2011	44	Knees/hips	Not described	?
Puhto[25] 2014	107	Knees/hips	Not reported	94%
Murillo [26]2008	25	Knees/hips	Not reported	100%
Bejon [27] 2010	152	Knees/hips	"Gentamicin-impregnated cement was used for cemented implants and allograft bone was used if required."	83%
Tan [28] 2016	267	Knees/hips	Not described	78%
Mittal [29] 2007	37	Knee	Resistant organisms. Cemented in all, antibiotics in 33/37; 4 reinfections.	76%
Watts [30] 2014	111	Knee	Cemented; vancomycin and gentamicin (median 1 (0-2), 1.2 (0-2.4). Comparison between obese and non-obese patients.	80% (O) 97% (NO)
Mahmud [38] 2012	253	Knee	Not described	85%
Haleem [31] 2004	96	Knee	Cemented	93.5%
Kubista [32] 2012	368	Knee	Not described	84%
Hoell [33] 2016	59	Knee	Not described	93.2%
Brimmo [34] 2016	750	Knee	Not described	83%
Cha [35] 2015	76	Knee	Cemented, 1gm vancomycin	76%
Castelli [36]2014	50	Knee	Not described	92%
Pelt [37] 2014	49	Knee	Not described	75%

infection, loosening or mechanical failure at 10-year follow-up. The authors concluded that the method of fixation used for the femoral component during two-stage reimplantation surgery should be based on the surgeon's preference for fixation combined with the assessment of femoral bone stock [11]. On the total knee arthroplasty (TKA) side, Edwards et al. found that re-revision rates for aseptic loosening were comparable with three cemented and three cementless stem constructs. The reinfection rate was also comparable between cemented and cementless stems ($p = 0.86$). Their conclusion was that cementless diaphyseal-engaging stems had a lower rate of radiographic failure than cemented stems in two-stage reimplantation. Reinfection rates remained similar despite the absence of antibiotic cement in the cementless constructs [8]. Additionally, George et al. performed a systematic review on cemented versus cementless single-stage exchange for infected THA and found no difference in infection success rates [9].

At this time, it is not clear that antibiotic-impregnated cement is required at the time of reimplantation to increase infection cure rates. Aminoglycosides and glycopeptides are known to be the two groups of antibiotics that qualify equally for incorporation into bone cement [12]. The combination of these antibiotics has the advantage of a wide antimicrobial spectrum with good elution kinetics [12]. Vancomycin is good for treating orthopaedic-related infections since Staphylococci are the most common bacteria causing such infections, and vancomycin possesses an excellent efficacy against these strains, especially resistant strains [12]. Generally, low-dose antibiotic-impregnated bone cement is defined as ≤ 4 gm antibiotic(s)/40 gm polymethylmethacrylate (PMMA) and it is used for reimplantation as higher doses affect the mechanical properties of cement [12]. If a clear benefit on infection cure rate is demonstrated by the use of antibiotic cement, further research will be required to determine the optimal antibiotic choice and dosage.

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QUESTION 2: Does the use of tantalum (Ta) augments during a single-stage revision for periprosthetic joint infection (PJI) influence the rate of surgical site infections (SSIs) or PJIs?

RECOMMENDATION: Findings of retrospective studies suggest that tantalum augments might have a protective effect against subsequent infection following single-stage revision joint in the context of PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 58%, Disagree: 31%, Abstain: 11% (Simple Majority, No Consensus)

RATIONALE

The interaction between organisms and metals used in orthopaedic surgery has been the subject of debate and investigation. Sheehan et al. [1] showed that Staphylococcal species showed greater adherence to stainless steel compared to titanium (Ti) in a rabbit model. Trabecular metal (Ta-coated) has been a popular addition to the armamentarium of the revision hip surgeon. Because of its bioactive nature and ingrowth properties, Ta is being used in primary as well as revision arthroplasty components, with good to excellent early clinical results [2-3].

It has been hypothesized that Ta might protect against infection. Schildhauer et al. [4] found that *Staphlococcus aureus* was significantly less adherent to pure Ta when compared to Ta-covered stainless steel and commercially pure Ti and Ti alloy (T1 – 6AL – 4V). However, in this study *S. epidermidis* exhibited similar adherence behavior between these metals.

Schildhauer et al. [5] also examined human leukocyte activation in the presence of Ta compared to other orthopaedic materials. They found that the extent of leukocyte activation was directly related to surface roughness. Cytokine release and phagocytic activity were both increased in the presence of Ta-conditioned media.

In a retrospective clinical study of revision total hip arthroplasty (THA) using Ta or Ti implants, 144 hips were evaluated for which revision had been performed because of infection. Failure due to a subsequent infection was 3.1% (2 of 64) in the Ta group and 17.5% (14 of 80) for the Ti group ($p = 0.006$) [6]. In a study of revision total knee arthroplasty (TKA), Ta metaphyseal cones were implanted in 21 patients (16 aseptic and 5 septic). At a mean follow-up of 36 months, only one reconstruction was removed due to persistent infection and all metaphyseal cones showed evidence of stable osteointegration [7].The results of these clinical studies also suggest that Ta might be protective against infection following revision THA and TKA.

More recently, Harrison and colleagues [8] assessed the intrinsic antibacterial properties of Ta compared to Ti acetabular components in a well-designed and controlled in vitro study. They found no difference between the two metals in terms of resistance to colonization with *S. aureus* and *S. epidermidis*.

The results of reconstruction of acetabular defects using Ta augments have been encouraging in the early and medium term. Klatte et al. [12] performed a case-control study assessing the influence of Ta augments on reinfection rates in patients who had undergone single-stage revision THA for infection. This was a retrospective case-controlled study using cohorts that were well-matched, and infection was diagnosed based on accepted, standardized criteria. There were no significant differences in the duration of surgery, blood transfusion rates or antibiotic protocols used with each group. There was no difference observed in the reinfection rates in either group (two cases in each group). Although the findings of Klatte et al. are interesting, the numbers involved were small and the presenting center has a vast experience with single-stage revision hence surgical technique as well as multidisciplinary management with a dedicated specialist microbiologist might have contributed to these results as well.

The literature certainly suggests that Ta has potentially important benefits in the reconstruction of acetabular defects. However, there is no clear evidence that acetabular augments result in a reduced incidence of infection when used in single-stage revision THAs for PJIs.

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QUESTION 3: Is the use of highly porous tantalum (Ta) associated with reduced risks of surgical site infections/periprosthetic joint infections (SSIs/PJIs) recurrences in revision total joint arthroplasties?

RECOMMENDATION: There is some evidence to suggest that the use of highly porous Ta is associated with reduced risks of SSIs/PJIs recurrences in patients undergoing revision total joint arthroplasties, particularly for treatment of PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 51%, Disagree: 36%, Abstain: 13% (Simple Majority, No Consensus)

RATIONALE

Cementless acetabular components are increasingly being used in complex revision total hip arthroplasty (THA) procedures. These implants have demonstrated favorable outcomes when compared to their cemented alternatives, with lower rates of aseptic loosening, osteolysis, fractures and infections [1]. The cementless options for revision THA procedures are components made primarily from either titanium (Ti) or Ta. Trabecular metal (TM) (Zimmer Biomet, Warsaw, Indiana, USA) constructs are increasingly utilized in difficult reconstructive procedures, especially when significant bone loss is encountered. TM is a porous composite, comprised of a carbon skeleton coated with Ta. Porous Ta coatings have a number of advantageous characteristics: increased volume of tissue ingrowth due to high porosity (75-85%); comparable elastic modulus to trabecular bone (2.5-3.9 MPa) to reduce stress shielding and favorable frictional attributes ($\mu = 0.88$) to reduce micromotion [2]. The benefits of porous metal augments are the direct ingrowth of host bone, impossibility of resorption, avoidance of disease transmission and easy availability. It has been reported in the literature that reconstruction with Ta implants can result in superior outcomes when compared to other cementless components. These results are hypothesized to be related to the superior osseointegration and have been reported both in animal and clinical practice studies [2–4].

Short- to medium-term results of porous Ta components are promising when compared to their cementless counterparts [4,5]. Flecher et al. reported global survivorship of 92.3% at 64 months with no aseptic loosening encountered [6]. Similar results have been reported by Clement et al., with implant survivorship of 92% at 5 years and no cases of radiological loosening [7]. Encouraging results have also been seen when the follow-up period is extended; Whitehouse et al. reported survivorship of 92% at 10 years for their series of patients managed with TM augments in combination with a TM acetabular component [8]. Promising results have also been reported with the use of TM cup-cage constructs, with 5- and 10-year survivorship figures of 93% and 85% respectively [9].

Wegrezyn et al. from the Mayo Clinic published their randomized control trial (RCT) comparing porous Ta ($n = 45$) with porous-coated Ti ($n = 41$) acetabular cups for primary THAs, with a minimum 10-year follow-up. Both groups had excellent overall survivorship, with 100% of patients in the TM group exhibiting osseointegration and no cup revisions for osteolysis, radiolucency or aseptic loosening. One patient (2%) in the Ti group was revised for aseptic loosening at 12 years. Radiographic analysis at final follow-up identified radiolucent lines in 4% of TM cups and 33% of Ti cups ($p < 0.0001$), raising concerns about the potential for future cup loosening and revision [10]. This concern echoed the results from the Rothman Institute, who found a significantly greater number of lucent zones in the Ti group when compared to the Ta group ($p = 0.02$), in patients reported to have major bone deficiency (Paprosky 2C, 3A and 3B) [11]. Similarly, Jafari et al. reported excellent survivorship with no differences between the two groups [11].

Klatte et al. performed a retrospective case-control study and found that the use of tantalum augmentation during one-stage exchange for infection had no effects on the incidences of reinfections or any other short-term complications. Average follow-up was only 3 years in both study groups, and the authors recommended further study to assess long term durability [12].

It has been reported that Ta, as a material, may have the ability to resist the development of infections better than Ti. A recently published retrospective case series involving 966 patients demonstrated lower rates of reinfections in cases revised for infection using Ta compared to Ti acetabular components [13]. The incidence of all-cause failures in the Ta group was lower than that for the Ti group (4.4% vs. 9.9%, $p < 0.001$). The results were more impressive in the cohort of hips revised for infection ($n = 144$). The failures due to reinfections were significantly lower in the Ta group compared to those in the Ti group (3.1% vs. 17.5%, $p = 0.006$). Three hypotheses were proposed to account for this observation:

I. Ta has a higher potential to stimulate osseointegration than Ti, and hence "dead space" is eliminated more rapidly; in addition, osteoblasts may adhere and integrate onto the surface more easily, thus depriving access to infecting organisms.

II. Due to the topographical three-dimensional structure of Ta, microbes may find it difficult to access and colonize compared to a flat surface, where a biofilm can easily be formed.

III. The chemistry or surface characteristics of Ta may be hostile to infecting organisms [13].

Adherence of bacteria to surgically used metallic implant materials is one of the most important virulence factors for local foreign body infections and a prerequisite for the development of biofilms on implants. An in vitro study from Germany tried to assess the differences between bacterial adherences to Ta vs. other commonly used orthopaedic metallic implant materials. Schildhauer et al. stated that pure Ta has a significantly lower *S. aureus* adhesion compared to Ti alloy ($p < 0.05$) [14].

An in vitro study from Sheffield et al. attempted to identify whether Ta exhibits any intrinsic antimicrobial or antibiofilm properties. Sections of both Ta and Ti were sterilized and then incubated with a low dose inoculum of either *Staphylococcus (S.) aureus,* or *S. epidermis* for 24 hours. Colony forming units (CFUs) were then quantified on Mueller-Hinton agar plates. No statistically significant differences were seen between the number of CFUs for either antimi-

crobial or antibiofilm activity in either group, thereby raising doubt regarding the latter two hypotheses stated above [15].

As the majority of reported studies are single-center with a limited study population, a large registry data approach may provide more insight. Matharu et al. reviewed the use of TM acetabular components in primary THA and compared their subsequent revision rates to non-TM coated prostheses [16]. The group performed a propensity score matched study from the National Joint Registry for England and Wales and report that five-year revision rates were significantly lower in the TM cohort compared to the control for: 1) all-cause (1.0% vs. 1.8%, $p < 0.001$), 2) aseptic acetabular loosening (0.1% vs. 0.2%, $p = 0.029$), and 3) infection (0.5% vs. 0.9%, $p = 0.001$) [16].

Laaksonen et al. report on a collaborative study by reviewing both the Australian and Swedish National Joint Registries in order to assess the risks of re-revisions between Ta and other cementless revision THAs. Included were 2,442 first-time THA revisions with porous Ta cups, and 4,401 first-time revisions with other uncemented cups. Survivorship with re-revision for any reason was comparable up to seven years between the two groups [86% (Ta) and 87% (control) ($p = 0.64$)]. Overall survivorship up to seven years with second revision for PJIs as the end-point was 97% for both groups ($p = 0.64$). Implant survival for a porous Ta cup in first-time THA revision was similar to the uncemented cup control. No benefits in survival with re-revision for infection as an end-point could be ascribed to the Ta group [17].

In summary, the results for the use of highly porous Ta components in revision THA procedures are promising with seemingly lower rates of PJIs than that for their Ti alternatives. The reasons for this reduction in infection rates are not yet known and more work needs to be done in this area.

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5.8. TREATMENT: SALVAGE

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QUESTION 1: Are there differences in outcomes and survivorship between knee arthrodesis (KA) and above-knee amputations (AKA) for chronic knee periprosthetic joint injections (PJIs)?

RECOMMENDATION: Yes, an AKA for the treatment of chronic PJI in total knee arthroplasty (TKA) has a lower functional outcome, and higher mortality rate than KA.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 82%, Disagree: 13%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

One of the earliest studies on the outcomes of the salvage procedures was published in 1988 by Pring et al. They reviewed 23 patients who were treated with AKA following a failed TKA and showed that more than half of the patients were ultimately confined to a wheelchair [1]. Isiklar et al. reviewed nine AKAs that were performed after failed multiple revision surgeries for TKA in eight patients. After an average 2.5 years of follow-up, only two out of nine patients were ambulatory with walker, and one patient required wearing a prosthesis. They

believed an earlier attempt at KA with preservation of bone stock can prevent poor outcomes of AKA [2]. Sierra et al. reviewed 18,443 TKAs performed between 1970 and 2000. They found that of 67 (0.36%) patients who finally underwent AKA, 19 of them were due to uncontrollable infection. The functional outcomes of patients undergoing AKA were poor, a substantial percentage of these patients were never fitted with a prosthetic, and those who were fitted with a prosthetic seldom obtained functional independence [3].

Blom et al., in a review of 69 revision cases, found a 5.8% infection rate. Two infected cases who underwent KAs demonstrated Oxford scores comparable with patients who were treated with two-stage revisions [4]. Fedorka et al. retrospectively reviewed 35 patients who underwent AKAs after infected TKAs. After a mean follow-up of 39 months, 15 of the patients receiving AKA had died and 11 patients needed repeat surgery. Only 8 of 14 patients who received prosthetics were able to regain functional ambulation [5]. Chen et al. retrospectively studied the functional capacity of 20 cases of patients undergoing KA, and compared them to 6 previously reported cases of AKAs for PJIs after TKAs. Both physical and mental components of the Short Form-12 (SF-12) questionnaire were higher in KA group. The number of community-ambulators increased in KA group and decreased in the AKA group. They concluded that KA as treatment for recalcitrant PJIs after TKAs may have better functional outcomes compared to performing an AKA [6]. Khanna et al. found nine patients who underwent AKAs for recurrent PJIs in TKAs from 2000 to 2013. They studied their functional abilities with SF-12 and asked patients about their satisfaction through developing a questionnaire. Six of seven patients were fitted to a prosthesis and four were able to wear the device more than one hour. Despite having poor functional outcomes, all patients were satisfied with their AKA compared to their preoperative situation. They recommended considering an AKA in chronically infected prosthetic knees in patients with multiple medical comorbidities, failed multiple attempts at revisions, soft tissue compromise of the knee and excessive bone loss or severe vascular disease [7].

Rodríguez-Merchán et al. in a review of 10 papers comparing AKAs vs. KAs after failed TKAs, found that a substantial percentage of the AKA patients were never fitted with a prosthetic and those who were fitted seldom obtained functional independence. They also reported that only 50% of patients were able to walk after AKAs, while KA patients could walk at least inside the house and activity of daily living independence was achieved by majority of the arthrodesis patients. They concluded that since functional outcomes after AKA are poor and KA patients have better function and ambulatory status, KA should be strongly considered as the treatment of choice for patients who have failed treatment for infected TKA [8].

Johnson and Bannister reviewed a small series of 25 knee infections and reported that KA was the most successful treatment modality for achieving pain relief and infection control in 11 of 12 (92%) patients at final follow-up [9].

One of the rare reports on unsatisfactory outcomes of the KA was published by Rohner et al. They reported a 50% rate of persistent infection and a 73% persistent pain in 26 patients who underwent KA with intramedullary (IM) nail. All scores showed marked impairment of quality of life. They concluded that IM nailing following septic failure of revision TKA must be regarded with skepticism [10].

Carr et al. reported on patients in a national database spanning from 2005 to 2012 and found 2,634 patients with KAs and 5,001 patients who underwent AKAs for infected TKAs. They detected an increasing trend towards AKA rather than KA in patients who were older and had a greater number of comorbidities. They also found more common systemic complications, longer hospital stays, higher 90-day readmissions and more in-hospital mortalities after AKA. Arthrodesis cases, however, had significantly higher rates of postoperative infections [11].

Son et al. identified 1,182 KA and 1,864 AKA patients among a cohort of 44,466 patients who underwent revision surgery with diagnoses of infected TKA from 2005 to 2014 using The Medicare 100% National Inpatient Claims Database [12]. Their goal was to determine the frequency, risk factors associated with, and mortality of KA and AKA. They found decreasing trends toward AKAs and KAs since 2005. Clinical factors associated with arthrodesis included acute renal failure, obesity and having additional infection-related revisions. Higher Charlson comorbidity scores, obesity, deep vein thrombosis and additional revisions were factors associated with AKA, which in turn was an independent risk factor for mortality. After adjusting for age, comorbidities and other factors, mortality was higher in AKA patients. The risk of death in KA group did not change compared to patients who underwent revisions [12].

George et al. reviewed 53 cases of AKAs performed for PJIs after TKAs in order to identify the factors predicting ambulatory status after AKAs for PJIs of the knee and to elucidate the effects of this procedure on general health outcomes. After 29 months of follow-up, 43 patients were alive and 28 were available to be contacted. Fourteen patients had infection at the site of stump. A total of 47% of the patients were non-ambulatory and their functional outcomes did not improve compared to their pre-amputation status. Male gender and preoperative community ambulatory status were independent predictors of walking ability after AKA [13].

Hungerer et al. compared functional outcomes, complications and qualities of life between 81 modular KAs and 32 AKAs performed for PJIs after TKAs between 2003 and 2012, with the use of the Lower-Extremity-Functional-Score (LEFS) and the patient reported general health status (SF-12) questionnaire. After a mean interval of 55 months, recurrence of infection was higher in AKA patients (35% vs. 22%). Patients with AKAs and modular KAs showed comparable functional outcomes and qualities of life. Notably, 10 AKA patients that could be fitted with a microprocessor-controlled knee joint demonstrated significantly better functional outcomes than other amputee patients ($p < 0.01$) or modular KA patients ($p < 0.01$). The group concluded that the AKAs should be considered as an option in patients with a good physical and mental condition [14].

Wu et al. performed a systematic review of the literature and a decision analysis to determine the treatment modality likely to yield the highest quality of life for a patient after a failed two-stage reimplantation procedure of an infected TKA. Consistent evidence in the majority of case series and reviews supported that lower functional outcome and higher mortality are expected following AKA compared to KA after failed infected TKA. Based on the data, the authors concluded that KAs should be strongly considered when patients present with failed two-stage revision for infected TKA. KA is most likely to provide infection control while maximizing patient function when there is sufficient residual bone stock and when a repeat two-stage reimplantation procedure has low likelihood of success (i.e., resistant organisms, poor host and inadequate soft tissue envelope) [15].

Kohn et al. performed a review of the literature over a 10-year period. They found that KA after failed infected TKA was a difficult procedure that was associated with complications. The review revealed that bone loss of the distal femur and proximal tibia was the most important prognostic factor [16].

Additionally, in a recent article Parvizi et al. declared that complete eradication of recalcitrant PJIs can be achieved by resection of all components without reimplantation through KA or AKA. They concluded that innovations in the future such as transcutaneous prosthetic fitting may provide an improvement on what we have and allow patients with AKA to achieve functional independence [17].

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QUESTION 2: How many exchange arthroplasties are reasonable before a salvage operation (such as amputation or arthrodesis) should be considered?

RECOMMENDATION: Patients with a failed two-stage exchange arthroplasty that undergo a repeat two-stage exchange arthroplasty demonstrate poor outcomes. Failure of the repeat two-stage exchange arthroplasty appears to be dependent on the host grade and status of the extremity. Surgeons thus should consider the patient's comorbidities and expectations when deciding whether to subject the patient to repeat two-stage exchange arthroplasties. The outcomes of a third or fourth two-stage exchange arthroplasty are dismal.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 88%, Disagree: 10%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Two-stage exchange arthroplasty remains the preferred method of treatment for chronic periprosthetic joint infections (PJIs) in the United States. The reported success rate of two-stage exchange arthroplasty is variable with rates ranging from approximately 70 - 90%. However, there is significant morbidity and mortality associated with undergoing multiple surgeries for management of PJIs [1,2]. Furthermore, these patients are often very fragile and poor hosts.

There are several studies in the literature demonstrating poor outcomes after the initial failed two-stage exchange arthroplasty. Kheir et al. found that in patients undergoing a second two-stage exchange arthroplasty, reimplantation occurred in only 65% of cases and successful outcomes occurred in only 61.6%. Furthermore, of the 14 cases that were not reimplanted, there was a high rate of retained spacers (n = 6), amputations (n = 5), PJI-related mortalities (n = 2), and arthrodesis (n = 1) [3]. Kalra et al. reported on a similar cohort where success was achieved in 36.4% (4/11) of patients that underwent re-revision after a prior failed two-stage exchange arthroplasty [4].

Azzam et al. demonstrated that recurrent or persistent infections after a failed two-stage exchange was found in 4 out of 18 patients (22.2%) [5]. In this series, two patients underwent a third two-stage exchange arthroplasty and both were infection-free at two years. Furthermore, Fehring et al. found that in 45 patients undergoing a second two-stage exchange arthroplasty, 22 (49%) had another revision for reinfection [6]. The latter study also evaluated the risk factors for failure and found that poor host and extremity grades were associated with an increased risk of failure. When stratified by host grade, revisions for reinfections were performed in 30% of the uncompromised hosts (type A), 48% of the medically compromised hosts (type B) and 75% of the very medically ill patients (type C). In addition, Backe et al. also investigated the outcomes of 12 patients that failed an initial two-stage exchange arthroplasty, including 9 patients treated with a repeat two-stage and 3 patients treated with an arthrodesis. While there were no instances of reinfections in either group, the three solid fusion patients were dissatisfied with their stiff limb despite its good position [6]. In patients with a failed repeat two-stage exchange arthroplasty, the organism identified is most often different than that identified in the initial two-stage exchange [6].

While the outcomes of a second two-stage exchange arthroplasty are well known, there is minimal literature regarding the expected outcomes of a third and fourth two-stage exchange arthroplasty. However, understanding the risk factors for failure after an initial two-stage exchange arthroplasty may help determine which patients are optimal candidates for additional two-stage exchange arthroplasty attempts. In patients with increased comorbidities, infection with resistant organisms, or an organism associated with

poor outcomes (e.g., fungal or enterococcus PJIs) salvage procedures should be considered.

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QUESTION 3: What are surgical alternatives to hip disarticulation in patients with persistent joint infections?

RECOMMENDATION: Surgical alternatives to hip disarticulation include resection arthroplasty when reconstruction of the joint with the use of a megaprosthesis is not possible. Hip disarticulation should be reserved for patients with systemic sepsis and/or extreme soft tissue infections of the extremity, in whom the surgery is performed as part of a life-saving procedure.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 4%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Hip disarticulation is considered a last-resort option for non-neoplastic indications including necrotizing soft tissue infections, gas gangrene and life-threatening infections [1]. Fenelon et al. [2] reported on 11 cases of hip disarticulations performed as a result of failed arthroplasties due to severe infections of soft tissues and bones, bone stock losses or vascular injuries.

The extensive loss of bone stock from failed arthroplasty procedures and revisions is a major challenge with or without infection. Fountain et al. [3] identified 14 patients who had a total femoral arthroplasty as a limb salvage procedure after complications following revision arthroplasty surgery over a 25-year period. The indications for treatment included eradication of prosthetic joint infection (PJI), treatment of infected periprosthetic fractures, massive bone loss precluding the use of stemmed prosthesis, recurrent dislocation or a combination of these factors. Six patients had no complications. Three patients developed an infection and five patients sustained repeated postoperative dislocations. Eight patients had no pain, whereas eight other patients had persistent pain necessitating prolonged opioids. There was an overall improvement in function in all patients with four patients achieving a 75% improvement.

Parvizi et al. [4] reviewed 48 patients who received a modular megaprosthesis with or without bone grafting. There were good functional outcomes in 22 patients, fair results in 10 patients and poor results in 11 patients. Three patients had died before the minimum 2-year follow-up had elapsed. They concluded that for patients with severely compromised bone stock precluding the use of conventional prostheses due to inability to achieve adequate fixation, this might be a viable salvage procedure for these patients.

Smolders et al. [5] reviewed 25 patients in a retrospective study treated with the Modular Universal Tumor and Revision System (MUTARS®); Implantcast GmbH, Buxtehude, Germany). Harris Hip Scores improved from 28 points preoperatively to 81 points postoperatively, with 24% of patients developing complications.

Berend et al. [6] reported on 59 patients that had total femoral arthroplasties for salvage of end-stage prosthetic diseases. Indications for the procedure included numerous revision total hip or knee arthroplasties, failed periprosthetic femur fractures or recurrent infections treated with multiple radical debridement surgeries. Mean follow-up was 4.8 years. The average Harris Hip Pain Score was 34 out of 44 points. Good function was achieved with 98% able to ambulate and 43% using an assistive device or cane. There were 18 complications or subsequent surgeries (30.5%). Infection occurred in eight patients and dislocations in seven patients.

Shih et al. [7] evaluated 12 patients with massive proximal femoral deficiencies who received a proximal femoral megaprosthesis for failed total hip arthroplasty (THA). They had a mean follow-up of six years. Eight (67%) patients had satisfactory results, one had a fair result and three had poor results. The complication rates were high with dislocations in five (42%), deep infections in four (33%), ectopic ossifications in one (8%), one displacement of the greater trochanter and one case of aseptic loosening. Three patients had permanent resection arthroplasty procedures for recurrent infection.

Artiaco et al. [8] reported on five patients with severe femoral bone loss and infection using a megaprosthesis in the revision of infected THA. They compared their results to four studies using megaprosthesis for a severe femoral bone loss and infection. One of the studies was inadequate for data and three were used for comparison. Their results were four out of the five patients had eradication of their infection and Harris Hip Mean Score of 74 points compared to 20 cases from three literature studies of 75 points. The literature review group had 6 (33%) patients with recurrent infections and overall complications in 8 of 20 (40%). They stated that revision with a megaprosthesis in cases of infected total hip arthroplasties with severe femoral bone loss have a high risk of complications and should be carefully evaluated and used in selected patients when other surgical procedures are not feasible.

Friesecke et al. [9] evaluated the results of total femur prostheses implanted during revision arthroplasty in 100 consecutive patients without infections. The mean duration of follow-up was five years. Sixty-five patients (68%) had no complications. Deep infection occurred in 12 patients (12%), material failure in 3 and peroneal palsy in one (1%.). The mean Enneking hip function score was 1.25 points preoperatively and improved to 3.29 points postoperatively. The mean preoperative Enneking knee score was 2.09 points and 3.29 points postoperatively. They concluded that total femur arthroplasty (TFA) is a useful implant for patients with extensive bone losses at revision arthroplasty. Although the infection rate was high, the overall functional results were rated better than good by the Enneking classification for the hip and knee.

Gebart et al. [10] reported on 45 patients undergoing revision surgeries using the MUTARS® (Implantcast GmbH, Buxtehude, Germany). The average follow-up was 39 months. Complications occurred in eight patients (18%) with one dislocation, two aseptic loosenings and five reinfections. The Harris Hip Score was 3.0 presurgical and 78 postsurgical. Castellanos et al. [11] reported on the results of 78 patients at 5-year follow-up with infected hip arthroplasties who underwent resection arthroplasty procedures. A total of 86% of patients had infections controlled and satisfactory pain relief was achieved by 83% of patients.

Ganse et al. [12] reported on 18 hips with a mean follow-up of 52 months. Thirteen hips had two-stage revisions and five patients had an excisional arthroplasties. They reported no differences in the Harris Hip Scores between the two groups, with a mean score of 60 points. Cordero-Ampuero et al. [13] reviewed the results of resection arthroplasty procedures in the literature concluding that there was wide variability in satisfaction ranging from 13-83%. Resolution of infection occurred in anywhere from 80-100% of patients. Risk factors for failure included rheumatoid arthritis, methicillin-resistant *Staphylococcus aureus* (MRSA) and enterococcal infections and retention of cement. Pain was reported as severe in 16-33% of patients, moderate in 24 - 53%, and mild in 76%. Twenty-nine percent were able to walk independently, and 45% of geriatric patients were unable to walk. Harris Hip Scores ranged from 25 to 64 points.

Korim et al. [14], in a systemic review of proximal femoral arthroplasty (PFA) for non-neoplastic conditions, reported on 14 studies with an average of follow-up of 4 years (range 0-14 years) describing 356 PFAs. Complications most commonly occurring were dislocation (15.7%) and infection (7.6%). The mortality rate ranged from 0 to 40%.

In conclusion, several alternatives to hip disarticulation exist, including the resection arthroplasty and the implantation of megaprosthesis such as proximal and total femoral arthroplasties with or without allograft. However, the efficacy and indications of these procedures remains unclear due to low-level evidence and short-term follow-up. Further higher-level studies are required to better guide treatment in these complex clinical settings.

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5.9. TREATMENT: ANTIMICROBIALS

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QUESTION 1: What is the recommended duration of antibiotics after a single-stage exchange for periprosthetic joint infections (PJIs)?

RECOMMENDATION: In the setting of single-stage exchange arthroplasty, intravenous antibiotics should be administered for 10-14 days followed by oral antibiotics. Generally, the overall duration of antibiotics of 4-6 weeks is sufficient.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 73%, Disagree: 23%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

The two-stage exchange arthroplasty is the preferred method for treatment of chronic PJIs. However, the single-stage exchange procedure has been gaining popularity, demonstrates comparable outcomes regarding infection control and offers various benefits for

patients compared to two-stage exchange [1–3]. Unfortunately, there are limited studies examining the issues of antibiotic administration following one-stage exchange arthroplasty. In addition, the duration of antibiotic treatment after two-stage exchange arthroplasty is not well determined either.

Most studies related to one-stage exchange arthroplasty highlight the importance of preoperative identification of the infective organism [4–11]. This is important for numerous reasons, including the ability to add the appropriate antibiotics to polymethyl methacrylate cement during reimplantation as well as administering the appropriate antibiotics after the procedure. Antibiotic therapy following single-stage revision surgery usually starts with an intravenous agent based on the antibiogram of the infective agent. Intravenous antibiotics are usually administered for a few days and then replaced by oral agents if available. In the postoperative period, antibiotics are adjusted to the susceptibility reports from intraoperative samples. In a Similar fashion to two-stage exchange arthroplasty, antibiotics are selected in accordance with organisms and sensitivities and are subsequently continued for four to six weeks [6,10,12–14].

Some authors continued the antibiotic therapy until inflammatory markers (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) as well as nutritional markers, such as plasma albumin concentration, return to stable limits (levels normalized in 90% of cases) [10]. Normal levels for serological markers are thought to be an ESR of 30 mm/hour, CRP of 10 mg/L, and albumin of 35 to 50 gm/L.

Other investigators believe that the type, course and duration of antibiotic treatments for patients undergoing one-stage exchange arthroplasty needs to be determined by a designated infectious disease consultant [4]. In this study, the average duration of the antibiotic treatment was 14 days (range, 10-17 days). Duration was determined by wound healing and laboratory infection parameters. No prolonged oral antibiotic therapy was administered in all 70 cases.

The importance of the local delivery of antibiotics during one-stage exchange arthroplasty has not been well studied. Some surgeons, including those at the HELIOS ENDO-Klinik, believe that the addition of antibiotics to cement during reimplantation plays a major role in infection control. There are two studies that point to the potential importance of antibiotics in cement [12,15]. In the latter study, the infection free rate was under 60% for patients undergoing one-stage exchange arthroplasty. Culture-specific antibiotics were given for at least six weeks to all the patients, but the single-stage exchange arthroplasty was performed with cementless total hip arthroplasty without local antibiotics. It is important to mention that the findings of low infection control could relate to other factors (e.g., how the surgery was performed) and may not be related to local antibiotic delivery at all.

Despite the paucity of concrete evidence with no randomized clinical trials available on the subject of antibiotic treatment after one-stage exchange arthroplasty, the use of antibiotic therapy following single-stage revision procedure is a universal practice. However, there is a lack of evidence for the duration of therapy. Currently, the orthopaedic community feels that a few weeks of antibiotic treatment, following one- or two-stage exchange arthroplasty is needed. Whether this will stand the test of time remains to be seen. In the absence of evidence to the contrary, we believe that patients undergoing one-stage exchange arthroplasty for the management of PJIs should receive four to six weeks of antibiotic treatment, which can be started as intravenous for a few days and switched to oral antibiotics soon after. We also feel that the dose, duration and type of antibiotic therapy should be individualized for most patients based on numerous metrics that influence the outcomes of treatment of PJIs, including the host type, organism virulence, the complexity of the procedure and soft tissue status.

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QUESTION 2: Are there any tests that can guide antimicrobial treatment in patients with periprostetic joint infections (PJIs) so as to determine when treatment may be discontinued?

RECOMMENDATION: No. There are no tests that can be used to guide therapies and monitor responses to treatments in patients with PJIs. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are considered useful for monitoring responses to treatments; however, sustained elevations after treatment does not predict persistent infections. Emerging biomarkers, such as D-dimer and presepsin, have shown promising results. Nevertheless, more studies are required to assess their role in monitoring response to treatment in patients with PJIs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 89%, Disagree: 8%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

The diagnosis of PJIs remains a challenge. Currently ESR and CRP are the most commonly used serological markers used for diagnosis. More recently, serum molecular biomarkers such as D-dimer and presepsin have emerged as potential diagnostic tools. However, determining whether the infection is controlled after surgical and antimicrobial treatment is even more difficult. There are limited studies assessing the roles of biomarkers in the follow-up periods of these patients; most of these studies have focused on diagnostic performance. No studies were found to specifically assess the role of biomarkers for guiding the antibiotic treatment protocols. However, there are studies that evaluate the roles of these markers in determining reimplantation timing and prognosis of PJIs.

Of the 11 published studies that were found to be relevant to this topic, 9 were prospective nonrandomized trials that focused on comparing the levels of biomarkers at the time of the diagnosis and reimplantation. These studies have shown that serum ESR and CRP are poor predictors of persistent infections and that they are frequently abnormal even when the infection has been controlled. New markers, such as the cytokines in synovial fluid, leukocyte esterase and serum D-dimer, tend to normalize at the time of reimplantation. However, more studies are required to show their trends with antimicrobial treatments.

Sanzén et al. studied the performance of serum ESR in 76 patients with PJI and found that in treated infections, ESR decreased to a lower value compared to the initial assessment [1]. In those with persistent infections there was a non-significant increase in ESR after 6 weeks, 3 months, 6 months and 12 months; the average ESR was above 30 mm/hr; and in resolved cases ESR was lower than 20 mm/hr. However, the authors did not take into account patients who had inflammatory diseases. Likewise, George et al. evaluated the values of ESR and CRP in 14 infected arthroplasties in patients with inflammatory arthritis, finding that these markers remained elevated in the infected group [2]. Shukla et al., Ghanem et al., Tornero et al., Hoell et al. and Kusuma et al., all showed that ESR and CRP remained elevated in more than one-third of cases in which the infection was eradicated, demonstrating that ESR and CRP often fail to normalize and do not reflect infection eradication [3–7].

Frangiamore et al. evaluated cytokine profiles of the synovial fluid between the first and second stage of a two-stage exchange protocol for PJIs in order to determine the cytokines that can indicate resolved infections [8]. The reimplantation (second-stage revision) was performed after symptom resolution, completion of antibiotic treatment (3-16 weeks, mean of 6 weeks), and normalization of CRP and ESR in addition to negative cultures by aspiration. Interleukin (IL)-1β and IL-6 had the best performance for determination of infection eradication.

Kheir et al. assessed the leukocyte esterase (LE) strip test for its ability to predict persistent infections in patients with PJIs [9]. Patients were evaluated at the time of reimplantation with the LE strip test, considering 2+ as a positive read. The LE test was negative in all reimplantations that did not fail. The authors found higher failure rates in those who had positive test results at the time of reimplantation.

A single prospective multicenter study by Marazzi et al. evaluated the trends of presepsin and chemokine (C-C motif) ligand 2 (CCL2) in 30 patients with PJIs [10]. The authors found a gradual decrease in the first week after surgery and reach values similar to the control group (patients without PJIs) in the first month and three months after the first revision. Another prospective study conducted by Shahi et al. evaluated the utility of D-dimer in the diagnosis of PJIs and also examined its role in determining the timing of reimplantation [11]. The authors found that serum D-dimer levels fell below the diagnostic threshold at the time of reimplantation in resolved cases. Furthermore, serum D-dimer was able to indicate the persistence of infection at the reimplantation time if the values were greater than 850 ng/mL (the recommended cutoff). Whether serum D-dimer levels can guide antibiotic treatment and have a consistent trend in response to antibiotics remains to be evaluated.

In conclusion, there is no single test or a gold standard that can indicate infection eradication in patients with PJIs. Although there are several studies on biomarkers for diagnosis, studies on responses to antibiotic treatments in patients with PJIs are lacking.

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QUESTION 3: Does the International Consensus Group (ICG) agree with the Infectious Diseases Society of America (IDSA) guidelines regarding the recommended duration of antibiotic therapy in orthopaedic infection?

RECOMMENDATION: There is some disagreement between what the ICG and the IDSA recommends regarding the duration of antibiotic treatments for different infective organisms. The differences between the two organizations resides on the duration of oral antibiotic therapy following a pathogen-specific intravenous (IV) antimicrobial therapy.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 82%, Disagree: 3%, Abstain: 15% (Super Majority, Strong Consensus)

RATIONALE

The optimal length of antibiotic treatment following surgical treatment of periprosthetic joint infections (PJIs) by resection arthroplasty, one-stage exchange arthroplasty, or debridement and implant retention remains unknown. There are numerous studies related to this subject and during the last meeting of the ICG, it was felt that antibiotic treatments between two and six weeks appeared to be sufficient for patients with PJIs.

The last ICG found no conclusive evidence regarding the ideal duration of antibiotic therapy when considering treatment following resection arthroplasty due to PJIs. They found that the ideal duration of antibiotic therapy, either IV or combined with oral medications, was unknown. Cost and resistance were lower when decreasing the time of antibiotic regimens [1–6]. Most of the literature, at the time, recommended antibiotic therapy between 6 and 12 weeks, although Bernard et al. found that 1 week of an IV antibiotic regimen plus a following 5 weeks with oral regimen was sufficient to control infection. This study involved irrigation and debridement (I&D), single-stage exchange arthroplasty and two-stage exchange arthroplasties [4]. Stockley et al. used a short two weeks IV-only antibiotic therapy following I&D and placement of an antibiotic-impregnated cement spacer, and noted an 87% success rate [7]. Nevertheless, the ICG strongly recommends a course of two to six weeks of antibiotics.

The ICG then explored how the duration of antibiotic treatments could be determined, agreeing that there was not enough evidence to determine whether biomarkers or clinical symptoms could be used to monitor response to treatment.

Additionally, the ICG attempted to determine the duration for antifungal therapy in the presence of fungal PJIs. They strongly agreed upon consensus stated that systemic antifungal treatment should be initiated before resection, and continued for at least six weeks, and stopped before reimplantation, without a need (in most cases) to restart antifungal therapy. For Fluconazole, the literature had 3 to 6 weeks or more (in some studies even 26 weeks) before reimplantation, then no further treatment, or only 2 to 6 weeks more after reimplantation. For Amphotericin B, the duration was often found to be about six weeks before reimplantation [8–20].

IDSA Guidelines

The IDSA guidelines suggest no more than a 6-week course of antimicrobial therapy following resection arthroplasty for PJIs due to more virulent organisms such as *Staphylococcus aureus* [21].The IDSA recommends two to six weeks of pathogen-specific IV antimicrobial therapy combined with 300 to 450 mg of rifampin given orally twice daily. The treatment should continue with rifampin plus a companion oral drug (ciprofloxacin (A-I), or levofloxacin (A-II), or others for a total of three months for Staphylococcal total hip arthroplasty PJI, treated with one-stage exchange or with debridement and retention of the prosthesis. The IDSA recommendation for Staphylococcal total knee arthroplasty PJI is the same, but for a total of six months when treated with debridement and prosthesis retention.

For organisms other than Staphylococci, the IDSA guidelines recommends an initial course of pathogen-specific IV therapy for four to six weeks, or highly bioavailable oral antimicrobial therapy (B-II). Chronic suppression after fluoroquinolone treatment of gram-negative bacilli was not unanimously recommended [21]. Longer courses of combination antimicrobial therapies of six months or more are recommended by the current guidelines and reports for bone infections due to rapidly growing mycobacteria (RGM) [22,23].

IDSA guidelines recommend a minimum of six weeks of antifungal therapy for fungal PJIs, but a longer course of antifungal therapy has been considered to be an essential factor for the success of fungal PJIs treated with staged reimplantation. Phelan et al. administered antifungal therapies after resection arthroplasty for six weeks to nine months in four patients who underwent two-stage reimplantations [8].

Regarding the IDSA guidelines on the treatment of osteomyelitis due to invasive Candidiasis, they recommend treatment duration from 6 to 12 months.

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QUESTION 4: Is the type, dose, route of administration and duration of antimicrobial treatment influenced by the type of infective organism causing periprosthetic joint infection (PJI)?

RECOMMENDATION: The duration, dose, route of administration and the type of antibiotic administered to patients with PJI is determined by the type of infective organism(s) isolated.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 4%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

There have been reports showing increased risks of treatment failure reported in patients with a sinus tract [1] and infections due to certain organisms such as *Staphylococcus aureus* [2], methicillin-resistant *Staphylococcus aureus* (MRSA) and gram-negative organisms [3–11] when not treated with a rifampin combination. For Staphylococcal PJIs, the Infectious Diseases Society of America (IDSA) guidelines recommend, based on expert opinion, two to six weeks of pathogen-specific intravenous (IV) antimicrobial therapy in combination with rifampin, followed by rifampin plus a companion oral drug for a total of three months [12].

The duration of antimicrobial therapy for most bacterial PJIs depends on the type of surgical procedure used to treat PJIs (debridement and retention vs. one-stage, vs. two-stage exchange, etc.) rather than the infecting microorganism itself.

One retrospective cohort study of 39 patients with PJIs undergoing single-stage exchange, of which 28 had Staphylococcal infections, demonstrated that two weeks of intravenous therapy followed by three months of oral antimicrobial therapy was sufficient to control the infection [13]. This study was limited by its small cohort size, lack of a control group and possible confounding variables.

The optimal duration of antimicrobial therapies in two-stage exchange arthroplasty is unclear. Multiple cohort studies have demonstrated acceptable cure rates in two-stage exchange arthroplasty with the use of six weeks to three months of total antibiotic therapy (IV and oral antibiotics) [14–19].

These retrospective cohort studies included a variety of infecting organisms, including *Staphylococcal* PJIs. These studies did not report any robust evidence that outcomes were worse for any organisms. There are no prospective trials directly comparing the duration of antibiotic therapy for Staphylococcal PJIs managed with two-stage exchange arthroplasty.

A retrospective cohort analysis of 30 patients with Streptococcal PJIs demonstrated high failure rates of 45%, in patients who underwent two-stage revisions [20]. The patients were managed with 2 weeks of IV antibiotics followed by 10 weeks of oral antibiotics.

Streptococcal infections are generally thought to be very responsive to treatment due to their broad antimicrobial sensitivity, including penicillins and cephalosporins. However, the high failure rate in this single-center study has not been further studied in other trials.

In the series reported by Eid at al., six of the eight patients with rapidly growing mycobacteria (RGM) PJIs received ≥ 1 active antimicrobial agent for at least six months [21]. In this series, the duration of effective therapy was as short as 16 weeks and as long as 55 weeks after resection arthroplasty, but other cases from other series were treated for as short as 3 weeks to as long as 112 weeks [22–28]. However, the optimal duration of antimicrobial therapy for RGM PJIs remains unknown. Shorter courses of three months for total knee arthroplasty (TKA) PJI, and two months for total hip arthroplasty (THA) PJI treated with debridement and retention of the prosthesis have been successful in 87.5% of the patients treated when compared to 89.5% of the patients in the same cohort treated with six months and three months respectively [29].

Rare cases of *Mycobacterium tuberculosis* and *Mycobacterium kansasii* PJIs required long courses of antimycobacterial therapies of 12-18 months [30,31]. The optimal medical and surgical therapies for *Mycobacterium tuberculosis* PJIs are unknown. Initial therapy should include isoniazid, rifampin and pyrazinamide, with the addition of ethambutol or streptomycin in case of suspected isoniazid resistance [32]. Management was successful in patients with unsuspected *Mycobacterium tuberculosis* PJIs incidentally discovered at the time of implantation or in the early postoperative period with non-rifampin anti-tuberculous combination therapies for 12-18 months [33,34].

Many authors favor a total of six months of antifungal therapy (fluconazole) that may start after resection arthroplasty and continue until after reimplantation, but a definitive duration of therapy has not yet been established [35–37].

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QUESTION 5: When a patient undergoes aseptic revision and intraoperative culture(s) grow an organism, should patients be treated with antibiotic therapy?

RECOMMENDATION: Antibiotic therapies are recommended if two or more cultures isolate the same organism, as per the MusculoSkeletal Infection Society (MSIS) and the International Consensus Group (ICG) criteria for prosthetic joint infections (PJIs). Antibiotic therapies may not be required when a single intraoperative culture isolates an organism. However, there may be circumstances when a single positive culture, combined with other tests, may indicate the presence of an infection and treatment would be indicated.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 8%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

It is important to evaluate patients undergoing revision arthroplasty for evidence of infection. Most of these evaluations are performed preoperatively. Revision surgery is then performed when the patient appears to be clear of an infection. The incidence of positive operative cultures in this setting varies extensively from 0-44% and the significance of these positive cultures is often uncertain [1-3]. Studies of the clinical outcomes of patients with positive cultures at revision surgery have been mainly retrospective and have limited and inconsistent conclusions [3-10].

If two or more operative cultures grow the same microbe, then treatment for PJI would be appropriate, as per the MSIS and the ICG criteria for the diagnosis of PJI [11,12]. However, if only one operative culture has bacterial growth, then the likelihood of a culture contaminant increases. An old but valuable study by Atkins et al. in the microbiology literature can be helpful in this analysis [13]. This prospective study found that when three or more operative cultures are obtained, a single positive culture reflected PJI due to that organism 13.3% of the time; two positive cultures were indicative of PJI in 20.4% of patients and three or more cultures positive for the same organism signified a PJI in 94.8% of patients. Based on this data, the risk of treating a patient with a substantial course of antibiotic therapy may well out-weigh the benefit if a single positive culture is associated with PJI in only 13.3% of cases. Patients in this category can be observed without antibiotic therapy, with an appropriately-timed, postoperative arthroplasty aspirate culture to help determine if the operative bacterial isolate is a contaminant rather than a true pathogen.

Other issues in the present literature which limit us in making solid conclusions include:

1. Lack of standardization of operative culture specimens to be submissions of tissues or fluids, but not swabs.
2. Need to analyze operative culture positivity occurrences with knowledge of the duration of the surgery. Revision arthroplasty surgery is usually of longer duration than primary implantation and intraoperative culture-positivity may only be a surrogate marker for the duration of the surgery, particularly if the operative cultures are obtained toward the end of the surgery.
3. A single operative culture which grows an organism, which was the pathogen treated for a patient's prior PJI, needs to be analyzed separately from those which grow a microbe that is unrelated to any previous infection. Further analysis may find that, whereas growth of a prior known pathogen represents persistence of true infection, growth of a single, entirely different organism is likely to be a contaminant.
4. Although difficult to perform, prospective, controlled studies are much more likely to result in solid conclusions than retrospective analyses.

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QUESTION 6: When should rifampin be added to the regimen of antibiotics for management of patients with periprosthetic joint infections (PJIs) undergoing surgical treatment?

RECOMMENDATION: Rifampin should be considered in the treatment of staphylococcal PJIs in patients managed surgically with debridement, antibiotics and implant retention (DAIR) or single-stage exchange where activity against biofilm is required. Rifampin should only be used in combination therapies, with the best reported combination appearing to be with a fluoroquinolone.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 96%, Disagree: 2%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

The excellent efficacy of rifampin against biofilm produced by staphylococci has been shown in vitro, in animal models and in patients with orthopaedic implant-related infections undergoing DAIR [1–8]. Nevertheless, rifampin should be used with care because of the danger of rapid emergence of resistance and potential unwanted effects, such as severe nausea, hepatotoxicity, interstitial nephritis and cytopenia [9,10]. Rifampin is a potent inducer of the cytochrome P450 oxidative pathway and can result in significant drug interactions [10,11]. Monotherapy is known to quickly promote rifampin resistance and must therefore be avoided [12,13]. The emergence of rifampin resistance in *S. aureus* is of particular concern [8,14]. The best documented combination partners for rifampin are fluoroquinolones [15,16].

Clinical data supporting the use of combination rifampin antimicrobial therapy and surgical debridement for the treatment of staphylococcal PJIs are available [14,17]. Widmer et al. showed in an open-label study that 9 of 11 patients (82%) with staphylococcal or streptococcal PJIs that could not undergo removal of hardware were successfully treated with rifampin in combination with either a beta-lactam or with ciprofloxacin [1]. A randomized controlled study by Zimmerli et al. showed that among 24 patients with methicillin-susceptible *Staphylococcus aureus* (MSSA), or coagulase-negative staphylococcus (CNS)-PJI, with stable implants and a short duration of infection managed with DAIR. Those able to tolerate long-term (three to six months) combination therapy with ciprofloxacin-rifampin achieved cure at higher rates than those treated with a ciprofloxacin-placebo [15].

Trebse et al. followed 24 patients with PJIs and retained implants prospectively over 4 years, showing 83% with a successful outcome. A total of 17 of the patients had Staphylococcal infections, and were treated with rifampin combination therapy; two of the four patients who failed had staphylococcal infections, one with methicillin-resistant *Staphylococcus aureus* (MRSA) and one with CNS [17].

Retrospective case series have described the success of rifampin combination therapy [10,14]. Successful treatments with rifampin-fluoroquinolone therapy was shown by Berdal et al. and Barberan et al. [19,20]. Rifampin, in combination with other antibiotics, including fusidic acid, vancomycin or daptomycin, has also been reported to be effective [21-23]. Many of the reported case series primarily address the successful treatments of MSSA and CNS infections. Barberan et al. observed a non-significantly ($p = 0.08$) higher failure rate in 7 MRSA-infected, as compared to 14 MSSA-infected patients. More important, in patients with a duration of infection ≤ 1 month treated with levofloxacin plus rifampin, the outcome was significantly better than that for patients with a longer duration of infection [24]. A cohort study by Peel et al. included 43 methicillin-resistant Staphylococcal infections (24 MRSA) and found 86% of patients were treated successfully, most with rifampin-fusidic acid. The found eight out of nine failures were in MRSA cases [25]. A retrospective multicenter study by Lora-Tamayo et al. reported on 345 *S. aureus* PJIs managed with joint retention, including 81 MRSA cases. A total of 88% of patients received rifampin combination therapy and failure rates were similar in MRSA (46%) and MSSA (44%) cases [26].

The Infectious Diseases Society of America (IDSA) PJI and MRSA management guidelines recommend the use of rifampin combination therapy (2-6 weeks of pathogen specific IV antimicrobial therapy plus rifampin followed by 3-6 months of rifampin plus an oral companion drug) in the treatment of staphylococcal PJIs/hardware infections in patients managed with debridement or single-stage exchange [27,28]. European guidelines include similar recommendations [29].

Unanswered questions regarding the role of rifampin remain; however, many clinical studies have focused on rifampin-quinolone combinations, with little information available for beta lactam-rifampin therapy. Of note, fluoroquinolone-resistant Staphylococci are found in many settings, especially in MRSA-strains [30]. The emergence of rifampin resistance can occur even when using combination therapies [8,25,26,31]. Drug interactions lowering the serum concentrations of companion antimicrobials, including fusidic acid and clindamycin, have been reported [32,33]. The clinical significance of these interactions, however, is still unknown. Additionally, the optimal duration of combination antimicrobial therapies, including rifampin, for the treatment of prosthetic joint infections with retained hardware is not yet known. While extended treatment (3-6 months) is recommended and often used, shorter treatment courses may be as effective in some settings [34].

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QUESTION 7: What is the optimal antibiotic therapy in cases of culture-negative (CN) periprosthetic joint infections (PJIs)?

RECOMMENDATION: In patients with true CN PJIs, the antibiotics should be selected to have broad spectrum activity against both gram-positive and gram-negative organisms. In addition, the exact choice should relate to the known modern epidemiology in that country.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 87%, Disagree: 6%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

In the literature, rates of CN PJIs vary from 0-42% but reports suggest that the outcomes are not necessarily worse than for culture positive cases if rigorous and robust pathways for diagnosis and management are followed [1–7]. Factors associated with increased risk of culture negativity include prior antibiotic use, delay in transportation of the samples to the laboratory and variations in culture techniques, including short duration of culture [1,8–11]. It is important to note that several studies demonstrate that administration of antibiotic prophylaxis prior to obtaining culture samples did not interfere with isolation of the infecting organism [12].

A recent systematic review by Yoon et al. evaluated clinical studies related to culture-negative PJI. After exclusions, seven studies were included in the analysis, with all studies being retrospective [1,4,6–8,12–15]. Of these, four studies defined PJI using MusculoSkel-

etal Infection Society (MSIS) criteria [6,13–15]. In the majority of these studies glycopeptides, such as vancomycin, were used followed by cephalosporins, beta-lactams, quinolones or combination therapy. The duration of intravenous antibiotics for CN PJI was usually six weeks. The investigators also noted that the use of antibiotics for CN PJI was accompanied with appropriate surgery, stating that the choice of surgical strategy greatly affects the treatment results of PJI. Most of the included studies reported that two-stage arthroplasty followed by 4-6 weeks of antibiotic therapy was effective with a success rate of 70-100%. Six of the seven studies in this review demonstrated similar success rates between culture-positive (CP) and CN PJI, with one reporting greater success for CN PJI [1,4,6–8,13–15]. The authors of the systematic review recommended that further studies are required to determine optimal therapy for patients with CN PJI. The latter systematic review did not include studies that have demonstrated a suboptimal outcome for patients with CN PJI [16–18].

A few recent studies have attempted to further explore the issue of CN PJI. Kang et al. reported on the challenges of selecting the appropriate antibiotics and the treatment of CN PJI was commenced with cefazolin and changed to glycopeptides if infection did not respond to the initial treatment [18]. Wang et al. also reported on the challenges of treatment for CN PJI [17]. They utilized intravenous vancomycin and/or an aminoglycoside for two weeks followed by an oral antibiotic such as levofloxacin and rifampin for an additional four weeks. A cement spacer containing vancomycin/meropenem was used in their cohort. In another study Peel et al. reported the use of vancomycin and cephalosporin followed by a broad spectrum oral combination comprising fusidic acid, rifampin +/- ciprofloxacin for a median of 7 months (3-20 months interquartile range) in the majority of the patients but choice of regimen varied by presentation [9].

In 2013 Marschall et al. published a survey in which members of the Emerging Infections Network were asked about current treatment of PJI. Regarding CN PJI, the vast majority of the responders chose a two-drug regimen in hip and knee infections, most commonly using vancomycin with ceftriaxone or vancomycin with oral fluoroquinolone as upfront antibiotic treatment [19].

In summary, it appears that the rate of CN PJI varies vastly from one study to another, perhaps reflecting the variability in definition of PJI, differences in culture techniques and the local epidemiology. Despite the presence of some studies demonstrating acceptable outcomes for CN PJI, the selection of optimal antibiotics for these cases remains challenging. The majority of reported series utilize a combination of antibiotics in the CN PJI. In an effort to reduce financial and psychological costs associated with optimal management of CN PJI, all efforts should be made to isolate the infecting organism. Similar to culture-negative endocarditis, zoonotic agents such as *Coxiella, Brucella, Bartonella* and *T. whipplei* are not easily detectable by the usual means and are not treated by common empirical agents such as glycopeptides [20]. A recent study has demonstrated that next generation sequencing (NGS) has a promising role in isolating the infecting organism in up to 90% of CN PJI cases [21]. Based on the emerging data, consideration should be given to the use of NGS or other molecular techniques in isolating of the infecting organism in patients with CN PJI. Serologies or serologic markers for certain zoonotic and endemic fungal infections should also be considered in the appropriate context.

If all attempts to isolate the infecting organism fail, then strategies employed in choosing an antibiotic regimen for CN PJI must be individualized based on risk factors, previous history and knowledge of the local epidemiology. The antibiotic treatment of CN PJI usually includes broad spectrum antibiotics with a prolonged intravenous phase. Glycopeptides play a pivotal role but consideration should be given to the use of multiple-drug regimens.

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QUESTION 8: What antibiotic therapy and duration of treatment should be used in Enterococcal periprosthetic joint infections (PJIs)?

RECOMMENDATION: Based on the limited available evidence, combination antimicrobial therapy should be considered for the treatment of Enterococcal PJIs, at least during the first weeks of treatment. Antibiotics should be tailored according to the susceptibility of the infective microorganism.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 85%, Disagree: 9%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Enterococci are often part of polymicrobial infections [1,2], have the ability to form biofilms [3,4] and thus can be difficult to manage [5]. *Enterococcus faecium*is listed as one of the ESKAPE (an acronym for *Enterococcus faecium, S. aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter spp.*) organisms, which are resistant to a majority of antibiotics available in our arsenal [6,7].

There is a lack of high quality randomized, controlled, prospective comparative treatment studies. However, based on the high failure rate of Enterococcal PJIs and the known limited bactericidal activity of ß-lactams on enterococci, some authors have suggested the use of combination antibiotic therapy for management of patients with enterococcal PJIs [8]. However, another study demonstrated that patients who received monotherapy had the same outcome as those treated using combination therapy regimen [9]. El Helou et al. described an 80% success rate using debridement, retention of the implant and intravenous ampicillin with or without gentamicin [9]. The success rate was similar in the monotherapy and combination groups, but nephrotoxicity was significantly higher among those receiving aminoglycosides. The results of the multi-institutional study by Kheir et al. support the former recommendation of combination systemic therapy [1]. Although the authors did not find statistical significance, there was a trend toward higher treatment success with combination antibiotic therapy. In addition, there is a high risk of selection bias in retrospective studies evaluating the efficacy of antibiotic therapy, as dual therapy is often applied in more severe infectious cases. The efficacy of dual theraphy in Enterococcal infections in clinical studies is primarily demonstrated for Enterococcal endocarditis. For monomicrobial non-resistant *E. faecalis* and *E. faecium* PJI, we recommend a combination of an intravenous cell wall synthesis-inhibiting agent (ampicillin or vancomycin, respectively) and to add gentamicin as a synergistic antibiotic, at least during the first two weeks of treatment, which is concordant with previous literature [1,5,10,11]. It is important to note that administration of a systemic aminoglycoside can increase the risk of nephrotoxicity and ototoxicity [9]. Other alternatives suggested in the literature to include as a synergistic antibiotic (instead of gentamicin) are ceftriaxone [12] or daptomycin [13-15]

Interestingly, it has also been suggested that rifampin in combination with other antibiotics may also lead to a lower rate of failure in early Enterococcal PJIs. Tornero et al. found that the administration of rifampin combined with other antibiotics was associated with a lower rate of failure than alternative antibiotics [16]. In addition, recent in vitro data showed that linezolid or ciprofloxacin combined with rifampin had better activity against Enterococcal biofilms than ampicillin or ampicillin plus rifampin; therefore, these combinations are potential alternatives [17].

Emerging antibiotic resistance, specifically to vancomycin, is a challenging problem for the management of Enterococcal PJIs [5,18]. Plasmid-mediated resistance to vancomycin was first described in 1986, and shortly thereafter numerous reports of the vancomycin-resistant *Enterococcus* (VRE) species appeared in the literature [19]. VRE species are phenotypically and genotypically heterogeneous, and among all of these phenotypes and genotypes, VanA resistance phenotype has been most commonly investigated [19]. For VRE, the literature suggests the use of either linezolid (with or without rifampin) [17] or daptomycin [1,20]. Although linezolid-resistance has been reported, fortunately at present there is no report of emerging daptomycin-resistant *Enterococcus* [21–24].

Polymicrobial infections are challenging to treat, as administration of multiple antibiotics is often needed [25]. For polymicrobial infections, broad-spectrum coverage should be performed. Literature is sparse on the use of oral antibiotics for patients with polymicrobial enterococcal PJIs, and it is not known if oral antimicrobial can be used for successful treatment of these patients.

The review of the available literature revealed that there was a high variability of antibiotic treatment duration for Enterococcal infections and lack of analysis regarding treatment duration in the above studies. In the study by Kheir et al., each patient's antibiotic duration was listed, and the majority of patients had six weeks of antibiotic treatment (although the range was broad: from 4-36 weeks of duration) [1]. Duijf et al. reported three months of antibiotic treatment resulting in 66% of patients retaining their implants [26]. This may suggest that longer antibiotic treatment may be beneficial in Enterococcal PJIs;however, further study is warranted in this domain.

Based on the available literature, and our experience, we recommend that patients with Enterococcal PJIs should be treated with 6-12 weeks of antimicrobial agents, preferably in combination.

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QUESTION 9: What are the indications for utilizing fosfomycin, tigecycline and daptomycin, either instead of other antibiotics or in conjunction with other antibiotics, for the management of periprosthetic joint infections (PJIs)?

RECOMMDENATION FOR DAPTOMYCIN: Daptomycin is an alternative treatment for patients with PJIs caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

LEVEL OF EVIDENCE: Moderate

RECOMMENDATION FOR FOSFOMYCIN: Although there is no clinical experience using fosfomycin in PJIs, it could be considered in infections due to multi-drug resistant gram-positive (MDR-GP) or gram-negative bacteria (GNB) as a part of a combination regimen with daptomycin, rifampin or tigecycline when the microorganism is susceptible.

LEVEL OF EVIDENCE: Limited

RECOMMENDATION FOR TIGEYCYLINE: Tigecycline could be considered for the treatment of MDR-GP or -GNB as a part of a combination regimen when the microorganism is susceptible.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 4%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

Daptomycin

Daptomycin is a cyclic lipopeptide with concentration-dependent bactericidal activity against gram-positive microorganisms. It is highly active against *Staphylococcus aureus*, coagulase-negative Staphylococci, *Enterococcus faecalis* and *Enterococcus faecium*, including both planktonic and biofilm-embedded bacteria [1]. Daptomycin combined with gentamicin has been shown to have synergistic activity on intracellular *S. aureus*. Additionally, daptomycin seems to exhibit activity against the stationary-phase bacteria inside a biofilm [2–4]. Several animal models of foreign-body infection demonstrated a high success rate with daptomycin but always in combination with rifampin [5,6].

Since its commercialization, several case series and one clinical trial have evaluated the efficacy of daptomycin in PJIs (Table 1). The first description [7] included 12 patients that received 4 mg/kg of daptomycin in monotherapy with a success rate of 45.5%. In addition, out of the five patients considered a success, only one retained the implant with oral suppressive therapy. Byren et al. [8] performed a

prospective, randomized controlled trial in PJIs treated with two-stage exchange to evaluate the safety and efficacy of 6 or 8 mg/kg of daptomycin in monotherapy for six weeks compared with the standard-of-care (vancomycin, teicoplanin or semisynthetic penicillin). A total of 75 patients were included and the clinical success rates were higher in daptomycin groups than in control group (58.3% for 6 mg/kg daptomycin vs. 60.9% for 8 mg/kg daptomycin vs. 38.1% for the comparators). The frequency of adverse events was similar in both groups; however, 16% and 22% of the patients in the 6 mg/kg and 8 mg/kg of daptomycin had increased creatine phosphokinase (CPK) levels (>500 U/L) vs. 8% in the control group.

In a retrospective study, Corona et al. [9] described 20 patients with PJI who received an average daptomycin dose of 6 mg/kg/day for a mean duration of 44.9 days. Fourteen patients were evaluated and four received rifampin (28.6%). The remission rate was higher than in previous studies (78.6%) and all patients treated with rifampin (including three acute PJI treated with debridement, antibiotic and implant retention (DAIR)) were in remission. Noteworthy, severe side effects occurred in two patients (10%) receiving daptomycin without rifampin and both required admission to the ICU. One developed a daptomycin-induced eosinophilic pneumonia and the other developed a massive rhabdomyolysis with acute renal failure. For this reason, authors recommended close monitoring for symptoms of myopathy with a weekly serial follow-up of serum creatinine. In addition, Jugun et al. [10] evaluated prospectively 16 patients with an osteoarticular infection treated with 8 mg/kg/day of daptomycin plus 600 mg of rifampin for a median duration of three weeks. Only six had a PJI but no clinically or laboratory-documented adverse events occurred that required adjustment or discontinuation of daptomycin therapy. All patients were in remission after an average of 15.8 (range 12.4-30) months of follow-up. Lora-Tamayo et al. [11] performed a retrospective, multi-centric study to evaluate the efficacy and safety of a 6-week course of daptomycin at 10 mg/kg plus rifampin in 20 patients with acute staphylococcal PJI managed with DAIR. Results were compared with 44 matched historical controls with PJI caused by fluoroquinolone-resistant staphylococci. The clinical failure rate was 50% in daptomycin group vs. 34% in historical controls (p = 0.265) and 29% and 30% had microbiological failure, respectively.

Malizos et al. [12] evaluated all patients with osteoarticular infection retrospectively collected from the European Cubicin® Outcomes Registry and Experience (EU-CORE) study that registered

TABLE 1. Summary of the clinical experience with daptomycin in PJIs including case series with more than five cases

Author, Year	Type of Study	Numberof Patients/ Type of PJI - Surgical Treatment	Dose, Duration	Rifampin (%)	Adverse Events Related with Daptomycin (%)	Follow-up Months (range)	MRSA n/Total (%)	Remission n/ Total Evaluated (%)
Rao 2006 [7]	P	12 / 5 early acute-DAIR 7 chronic-2S	4 mg/kg, 6 weeks	0	0	9 (range 7-13)	7/12 (58.3)	5/11 (45.5)
Byren 2012 [8]	RCT	75 / chronic-2S	6 mg/kg vs. 8 mg/kg vs. control, 6 weeks	0	CPK >500 u/L 6 mg/kg: 16% 8 mg/kg: 21.7% control: 8%	5-7	3/25 (12) 7/24 (30.4) 3/25 (12)	6 mg/kg: 14/24 (58) 8 mg/Kg:14/23 (61) control: 8/21 (38)
Corona 2012 [9]	R	20/ 8 early acute-5 DAIR and 3 2S 12 chronic-9 2S and 3 1S	6.6 mg/kg (median), 6.4 weeks	yes:8 (40)	CPK: 1 (12.5)	20 (range 12-41)	1/14 (7.1)	Acute infection: 5/6 (83.3) Chronic infection: 5/7 (71.4)
				no:12 (60)	CPK: 1 (8.3) Eosinophilic pneumonia: 1(8.3)			
Jugun 2013 [10]	P	16 osteoarticular infection (6 withPJI)	8.15 mg/kg (median) + rifampin 600 mg/d, 7.3 (range 2-17) weeks	16 (100)	0	15.8 (range 12.4-30)	3/6 (50)	totally or partially removed: 3/3 (100) DAIR: 3/3 (100)
Lora-Tamayo 2014 [11]	R	20 early acute-DAIR	10 mg/kg + rifampin 600 mg/d, 6 weeks	20 (100)	Rhabdomyolysis: 1 (5)	25 (range 24.4-32.3)	10/18 (55.5)	Daptomycin + Rifampin: 9/18 (50) Control group: 15/44 (34)
Chang 2017 [16]	R	16 / 5 early acute-DAIR 11 chronic-2S	8.3 mg/kg, 2 weeks	0	0	27	10/16 (62.5)	2S: 10/11 (91) DAIR: 4/5 (80)

P, prospective cohort; RCT, randomized control trial; R, retrospective cohort; PJI, prosthetic joint infection; MRSA, methicillin-resistant *S. aureus*; DAIR, debridement and implant retention; 2S, two-stage exchange; 1S, one-stage exchange.

real-world outcome data from patients receiving daptomycin. Out of 638 patients, 432 (67.7 %) had osteomyelitis and 206 (32.3%) had an orthopaedic device infection. More than 75% of the patients received ≥ 6 mg/kg of daptomycin during a median of 16 days (range, 1-176) for orthopaedic device infections. The remission rate was 81.8% overall and 85% in patients with PJI. Unfortunately, data about the type of infection (acute or chronic), methicillin-resistant *Staphylococcus aureus* (MRSA) rate and the surgical management was not reported. Overall, adverse events were reported in 78 (12.2%) patients, being severe in 39 (6.1%) and requiring discontinuation in 35 (5.5 %). The most recent report is a retrospective description of 16 patients treated with high doses of daptomycin (8.3 mg/kg per day) in monotherapy during a median of 14 days [13]. After this, all patients received oral antibiotics during a median of 35 days. The oral antibiotic combinations included were sulfamethoxazole/trimethoprim plus rifampin or fusidic acid plus rifampin. The study included 5 patients with an acute PJI treated with DAIR and 11 with a chronic PJI treated with two-stage exchange. It is important to highlight the high percentage of methicillin-resistant *S. aureus* (MRSA) (62.5%) and the high remission rate (87.5%). Specifically, there was one failure in acute PJIs (20%) and one among chronic ones (9%), both due to MRSA. No serious adverse events were reported.

In conclusion, a clinical trial showed that daptomycin at 6 or 8 mg/kg for six weeks had a higher cure rate than monotherapy with teicoplanin, vancomycin or a semi-synthetic penicillin. However, the clinical data suggest that ≥ 14 days of daptomycin in monotherapy is associated with adverse events (mainly CPK elevation). In contrast, other clinical studies combining daptomycin with rifampin did not observe problems with adverse events even after > 14 days of treatment and doses up to 10 mg/kg. This data suggests that rifampin could reduce the serum concentration of daptomycin (substrate of glycoprotein-P) but more data is necessary to support this hypothesis [13]. On the other hand, a short course of high dose (≥ 8 mg/kg) daptomycin without rifampin for the first two weeks of treatment followed by an oral rifampin combination seems to be well tolerated and associated with good outcome. Recent data show that the addition of daptomycin to cloxacillin or cefazolin may provide synergy, as shown by in vitro studies and animal experimental models [5,14]. This combination is promising to avoid the use of rifampin during the first 1-2 weeks of antibiotic treatment and to reduce the risk of selecting daptomycin-resistant mutants [15].

Fosfomycin

Fosfomycin has a broad-spectrum, including MDR-GP and (gram-negative (GN) microorganisms, a time-dependent bactericidal activity andis maintained in a low pH and in anaerobiosis [17–19]. Fosfomycin has a high bone penetration (bone:serum ratio of 43%), achieving concentrations above the minimum inhibitory concentration (MIC) for most susceptible bacteria [20]. There are three presentations: sodium fosfomycin for intravenous administration and trometamol and calcium salt for oral administration. Unfortunately, the oral bioavailability is < 20% for calcium salt and < 40% for trometamol. Therefore, only intravenous antibiotic is recommended for the treatment of bone infections [21].

Against GP, fosfomycin has demonstrated a potent in vitro synergistic activity against MRSA in combination with beta-lactams, daptomycin and linezolid. In addition, in an experimental foreign-body infection, fosfomycin combined with daptomycin or with rifampin were the second and the third regimens with the highest cure rate (defined as the percentage of eradication from the implant) only behind daptomycin plus rifampin and this was corroborated by other authors [22–26]. However, there is no clinical data supporting the efficacy of fosfomycin in PJI due to GP.

Fosfomycin has bactericidal activity in combination with carbapenems and colistin against carbapenemase-producing *Klebsiella pneumoniae* [27,28]. Corvec et al. [29] evaluated the activity of fosfomycin and tigecycline alone or in combination with other drugs against extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* strains in a foreign-body infection model. Fosfomycin was the only single agent for which the eradication of *E. coli* from cages was achieved and the combination that showed the highest antibiofilm activity was fosfomycin plus colistin, suggesting that fosfomycin should be considered in the treatment of MDR-GNB susceptible to fosfomycin strains. It is of note that fosfomycin could decrease the nephrotoxicity of aminoglycosides that in some occasions are the only active drug [30]. Although there is no clinical experience using fosfomycin in PJI due to GNB, it should be considered in infections due to MDR-GNB as a part of a combination regimen when the microorganism is susceptible.

Tigecycline

Tigecycline is active against GP and GN (except *Pseudomonas),* including vancomycin-resistant enterococci, MR-staphylococci, ESBL producing, carbapenemase (CP)-producing *Enterobacteriaceae* and *Acinetobacter* spp. Tigecycline has demonstrated synergistic activity against *Enterococcus* spp combined with rifampin and with amikacin or colistin against some MDR-*Enterobacteriaceae* spp, *Acinetobacter baumanii* or *Stenotrophomonas maltophilia* [31]. Data from foreign-body infection models due to MRSA showed that tigecycline in monotherapy was similar to vancomycinand in combination with rifampin was as effective as vancomycin with rifampin. Both options avoid the selection of rifampin-resistant mutants [32,33]. A recent study in healthy volunteers undergoing elective orthopaedic surgery demonstrated a good bone penetration after multiple doses of tigecycline (bone:serum ratio of 4) [34].

Clinical experience in osteomyelitis with tigecycline was documented in 13 cases with success in 85% but only one case was associated with an orthopaedic implant. In PJI the level of evidence is limited to a few case reports [35]. Vila et al.described three patients with early PJI of total hip arthroplasty due to MDR *A. baumannii* treated with debridement, implant retention and a high dose of tigecycline (100 mg every 12 hours) [36]. All patients received colistin concomitantly during a mean of 8.7 days and required at least one additional debridement, but all were asymptomatic after a median of 2.5 years. The major limitation for the prolonged use of tigecycline is the high frequency of nausea and vomiting. Vila et al. diluted tigecycline in 400 mL of dextrose and administered at a slow infusion rate in order to reduce the adverse events, and the therapy was well tolerated.

In contrast, de Sanctis evaluated three patients with a PJI due to carbapenem-resistant *K. pneumoniae* with poor outcomes [37]. All were polymicrobial infections, required multiple surgeries and complex antibiotic courses including tigecycline (two cases in monotherapy and one combined with amikacin first and with colistin later on). Prostheses were removed in two cases, but those patients died, and the one who survived required salvage limb amputation. In addition, resistant mutants to colistin and amikacin were selected while on antibiotic treatment however, the dose of tigecycline was not reported. Furthermore, Asseray et al. described four patients with PJI due to MDR- GP managed with implant removal and tigecycline during a median of 105 days (range 90-150) [38]. In addition, two patients received concomitant treatment with fosfomycin and one with linezolid. All patients but one (75%) were in remission after an average of 20.2 (range 14-32) months of follow-up. Only one patient treated with tigecycline plus fosfomycin experienced a moderate adverse event with anemia and thrombocytopenia, which was not

attributed with certainty to tigecycline; however, the dose of tigecycline was not specified. The rationale for increasing the dose (100 mg/12 hr) is based on its pharmacodynamic properties (area under the curve to minimum inhibitory concentration (AUC/MIC) ratio is the most predictive parameter related to clinical and microbiological efficacy), the presence of biofilms, and the multidrug-resistant profile of the involved organism [39]. Further experience and clinical studies are necessary, but tigecycline should be considered for the treatment of MDR-GP or GNB as a part of a combination regimen when the microorganism is susceptible.

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5.10. TREATMENT: ANTIMICROBIALS (TWO-STAGE)

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QUESTION 1: (A) What is the optimal length of administration for antibiotic treatment following resection arthroplasty? (B) What is the optimal mode of administration for antibiotic treatment following resection arthroplasty?

RECOMMENDATION: Antimicrobial therapy should be individualized and based on the sensitivity profile of the microorganism, patient tolerance and drug side-effect profile. There is no conclusive evidence supporting the exact length of antibiotic therapy after resection arthroplasty. We recommend treatment for two to six weeks. Either intravenous, oral antibiotics, or a combination are acceptable for treatment following resection arthroplasty as long as the oral agent has adequate bioavailability and can achieve a concentration at the site of infection to eradicate the infecting organism, if used alone.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 87%, Disagree: 9%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Treatment of periprosthetic joint infections (PJIs) with a two-stage revision arthroplasty remains a widely-used treatment strategy with success rates ranging from 72-94% [1–6]. The use of an antibiotic regimen after the initial explantation and placement of an antibiotic spacer is common; however, the optimal length and route of antibiotic administration has yet to be determined. Ensuring identification of the organism(s) prior to antibiotic therapy is critical for appropriate tailored treatment. Prior studies have shown that culture-negative patients that meet the MusculoSkeletal Infection Society (MSIS) criteria for PJI are difficult to treat and have been associated with 4.5 times increased risk of reinfection when compared to those patients where an organism was identified by culture [5,7]. In a recent study, culture-negative patients who met the MSIS criteria were investigated using next-generation sequencing and an organism was identified in 81.8% of samples, with the majority being low virulent organisms [8]. Understanding the infecting organism(s), the virulence patterns and their antibiotic susceptibilities by region are critical aspects to successful selection and chosen duration of antibiotics.

The literature has not found prolonged antibiotic therapy beyond six weeks to significantly increase success rates, and it may increase the rate of antibiotic related complications and expenses [9–11]. Many published studies have reported success rates ranging from 88-100% with a combination of oral and intravenous (IV) antibiotic administration of six weeks or less [6,12–18]. Bernard et al. found that the cure rate was no better with 12 weeks of antibiotics compared to 6 weeks for 144 knee and hip PJIs, including 74 resection arthroplasties [10]. Median IV antibiotic therapy was 10 days in the patients treated with two-stage exchange in this study [10]. Hsieh et al. evaluated the use of a total of 4-6 weeks of IV antibiotic therapy as compared to one week of parenteral antibiotic therapy in 99 two-stage revision total hip arthroplasty (THA) patients [14]. They found a 91% infection cure rate at final follow-up in patients treated with 4-6 weeks of antibiotic therapy and an 89% cure rate in patients treated for one week [14]. Treatment of antibiotic-resistant organisms for more than six weeks has also not been shown to improve outcomes. In one retrospective study, total knee arthroplasty (TKA) periprosthetic joint infection (PJI) patients infected with methicillin-resistant *Staphylococcus aureus* and streptococcal organisms had similar success rates with IV antibiotic therapy less than six weeks as compared to greater than six weeks when treated with a two-stage exchange [13].

To our knowledge, no published study has compared the efficacy of oral-only vs. IV-only antibiotics after resection arthroplasty, but a current study is underway [19]. Thus, antimicrobial treatment is mainly started with intravenous antibiotics in order to quickly achieve the appropriate concentrations locally. Once this initial postoperative scenario has improved, switching to oral antibiotic regimens is considered. Yet, an increasing number of clinicians and surgeons are using a combination approach of IV and oral antibiotics following resection arthroplasty, including some using rifampin as a companion drug [20–22]. Darley et al. described success in a small series of infected THAs using a median of 14 days of IV antibiotics (range, 12-28 days) followed by oral antibiotics for a median of 6 weeks (range, 2-25 weeks) before second-stage reimplantation, often in combination with rifampin [21]. Bassetti et al. described success with an "Udine strategy" following resection arthroplasty, particularly for gram-positive PJIs where an IV glycopeptide/lipopeptide plus rifampin is used for two weeks followed by four weeks of oral linezolid, and all therapy stopped at six weeks as long as two serial weekly C-reactive protein (CRP) levels are normal [20]. Currently, the Infectious Diseases Society of America (IDSA) recommends 4-6 weeks of pathogen-specific IV or highly bioavailable oral antimicrobial therapy following resection arthroplasty with an A-II recommendation [23]. However, many panel members would use six weeks of therapy for more virulent organisms such as *S. aureus* [23]. Similarly, an Italian guideline recommends that following resection arthroplasty, antibiotics be given 2-3 weeks parenterally, and 5-6 weeks orally with consideration of 6-weeks IV therapy without any retained foreign material for difficult-to-treat microorganisms [24]. Additionally, recent guidelines by the Spanish Society of Infectious Disease and Clinical Microbiology are similar to prior societal guidelines and recommend 4-6 weeks of pathogen-specific intravenous or highly bioavailable oral antimicrobials after resection arthroplasty [25].

In conclusion, there is no consensus on the exact length or route of antibiotic therapy in patients undergoing resection arthroplasty. The use of antibiotic therapy for 4-6 weeks after resection arthroplasty is supported by current studies and infectious disease societies. While some evidence has suggested an even shorter duration may be just as efficacious, further research will be required. A limited duration of IV antibiotic therapy may be indicated alone, in conjunction with oral antibiotics, or followed by oral antibiotics if organism-specific, highly bioavailable, oral antibiotics are available

for continued therapy and if agreed upon after discussion by a multidisciplinary team.

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QUESTION 2: Does extended oral antibiotic prophylaxis following reimplantation reduce the risk of future failure? If so, what type of antibiotic should be administered and for how long?

RECOMMENDATION: Possibly. There is emerging evidence that administration of three months of oral antibiotics directed towards the original infecting organism following reimplantation reduces the risk of early failure secondary to periprosthetic joint infections (PJIs).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 76%, Disagree: 18%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

PJIs are one of the most devastating complications following hip and knee arthroplasty and are associated with significant morbidity and mortality [1–3]. Several approaches have been used to treat this complication, one being a two-stage exchange arthroplasty with placement of an antibiotic-impregnated spacer followed by directed antibiotic therapy [4]. Hanssen et al. reported a 90% success rate with a two-stage exchange arthroplasty approach [4]. More recent studies have shown higher failure rates with this treatment modality due to reinfection with either the same or with a new organism [5–7].

To address the question of whether antibiotic treatment following reimplantation surgery had any effect on the subsequent failure rate, we conducted an extensive literature search. After removal of duplicates, 111 articles were found. After review of the abstracts, 52 additional articles were excluded. The remaining 59 articles were reviewed, among which 3 original scientific publications compared an extended course of postoperative antibiotics following a two-stage exchange.

All three studies were current, with publication dates ranging from 2011 to 2016. Study populations ranged from 66-107 patients. The highest quality study was a multicenter prospective randomized controlled trial. Two retrospective studies have evaluated the use of prophylactic antibiotics following reimplantation. Zywiel et

al. followed two cohorts of patients following a two-stage revision knee arthroplasty. Twenty-eight patients had a mean of 33 days of oral antibiotics (range, 28-43 days) following the reimplantation procedure and 38 patients received between 24 and 72 hours of post-operative intravenous antibiotics as standard prophylaxis. Patients were followed over a 12-month period and evaluated for reinfection. They found that the risk of reinfection with extended oral antibiotics was 4% compared with 16% in the control cohort that received routine perioperative antibiotics [8]. The single patient who was reinfected in the oral prophylaxis cohort was found to be infected with methicillin-resistant *Staphylococcus aureus*, which was present at the time of the original component removal. In contrast, a variety of low virulence organisms were the cause of reinfection in the group that received short-term prophylactic antibiotics intravenously. In a study by the same group that examined patients treated for periprosthetic hip infections, Johnson et al. found a 13.6% rate of reinfection in the perioperative antibiotic group compared to 0% reinfection in those patients treated with oral antibiotics for 14 days following a two-stage exchange [9].

There is presently one randomized controlled trial that reported the use of prolonged prophylactic oral antibiotics following reimplantation [10]. This multi-institutional study randomized patients to receive three months of oral antibiotics or standard prophylactic intravenous antibiotics only for up to 72 hours. This study included a total of 107 patients who were undergoing a two-stage revision hip or knee arthroplasty for a periprosthetic infection that met the MusculoSkeletal Infection Society (MSIS) criteria at the first stage and with negative cultures at the second stage. The rate of reinfection was 19% in the control group compared to 5% in the treatment group ($p = 0.0162$). Eight of the nine infections in the control group and one of the three in the extended oral antibiotic group were infections associated with a new organism. In the antibiotic cohort, three patients had to stop their antibiotic due to adverse reactions such as gastrointestinal upset and nausea. Three additional patients had minor adverse reactions such as rash or yeast infection; however, they continued to take the oral antibiotic despite these side effects.

Based on the available literature, there is moderate evidence to suggest that relatively short (three months) courses of oral antibiotic, following reimplantation after a two-stage exchange may reduce early failure with reinfection. All studies evaluating the role of antibiotic suppression have been short term and longer follow-up of the same cohort is needed as the one randomized trial did not report a full two years of follow-up for all enrolled patients. In addition, it is important to note that there were some issues with the administration of antibiotics and some patients had to discontinue the antibiotic. Administration of antibiotics under any circumstances needs to be weighed against its harm to the patient in terms of adverse effects and harm to society in terms of cost and its potential to cause emergence of resistant organisms.

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QUESTION 3: When is the optimal time to change intravenous (IV) antibiotic(s) to an oral agent(s) after a resection arthroplasty as part of two-stage exchange?

RECOMMENDATION: There is evidence to support pathogen-specific, highly bioavailable oral antibiotic therapy as an appropriate choice after resection arthroplasty in a two-stage treatment of periprosthetic joint infections (PJIs) after an initial IV antibiotic period of at least 5-7 days.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 83%, Disagree: 14%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Resection arthroplasty with a two-stage exchange is utilized in the management of PJIs in patients who are not candidates for a one-stage exchange, are medically able to undergo multiple surgeries and in whom the surgeon believes that replantation arthroplasty is possible [1]. An important part of the exchange arthroplasty includes administration of systemic antimicrobial therapy. The optimal time and the mode of administration of systemic antimicrobials has been the subject of numerous studies, with no definitive recommendations available.

Several studies recommend 4-6 weeks of pathogen-specific IV or highly bioavailable per oral (PO) antimicrobial therapy for patients with PJIs who have undergone two-stage exchange arthroplasty [1–3].

PJIs are usually treated with IV antibiotics in order to obtain the ideal plasma concentration in the shortest time possible. IV therapy requires an intravenous vascular access line that can be associated with infections and thromboembolic diseases [4]. Changing to PO therapy is less invasive for patients, lowers the financial burden and reduces hospital stay. Because of the aforementioned attributes of oral antibiotics, there has been an interest in identifying patients who may be candidates for administration of oral antibiotics.

Currently, there are no high-quality studies comparing different periods of initial IV regimens. An initial short course of IV therapy can reduce bacterial bioburden and minimize the risk of emergence of antimicrobial resistance [5–7]. Changing to PO therapy to complete the course of treatment has been shown to be effective. Darley et al. showed that 10-14 days of IV antibiotic therapy followed by 6-8 weeks of PO therapy was successful in 17 patients who underwent two-stage resection arthroplasty for management of prosthetic hip infections [8]. Ciriviri et al. and Ascione et al. showed high success rates with a similar approach [9,10]. Studies have also shown success with 5-7 days of IV therapy followed by PO therapy [11–13]. A fall in C-reactive protein (CRP) value was used to guide the timing for change in one study [14]. Observational studies using only shortened IV antibiotic courses in patients with antibiotic cement spacers have also reported success [15,16]. Of note, in examining the treatment of chronic osteomyelitis in adults, a Cochrane review of 5 small trials of 180 participants with bone or joint infection showed no benefit to IV therapy as compared to PO therapy [17].

Prospective, randomized clinical trials examining the role of PO antibiotic therapy for bone and joint infection are needed. The recently published results from the OVIVA (oral versus intravenous antibiotic treatment for bone and joint infections) trial was an important contribution. This study was a parallel group, randomized (1:1), un-blinded, non-inferiority trial conducted in 30 hospitals in the United Kingdom comparing PO to IV antibiotic treatments for bone and joint infections. Both arms had six weeks of either PO or IV antibiotics, and those selected for the PO arm had seven days or less of IV antibiotics at the start of treatment. A pilot of 228 participants that concluded in 2013 supported extension to the multicenter trial. The final analysis of 1,015 participants concluded that PO antibiotic therapy was non-inferior to IV therapy when used during the first 6 weeks in the treatment of bone and joint infections, as assessed by treatment failure within 1 year of randomization [18]. The study included 302 participants who underwent resection arthroplasty or implant removal. Additionally, a prospective study looking at extended PO antibiotics after second-stage (reimplantation surgery) showed a decreased rate of reinfection [19].

Given the availability of highly bioavailable PO antibiotic agents with good tissue penetration, the strategy of a shortened initial IV antibiotic course followed by pathogen-specific PO therapy should be considered following resection arthroplasty as part of two-stage exchanges. Additional prospective studies comparing outcomes to extended IV therapy should help clarify the optimal timing for transition. However, based on the available evidence it appears that oral administration of an antimicrobial, at least after a short period of IV treatment, is a viable option in treatment of some patients with PJIs and should be considered.

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QUESTION 4: Can short term (two weeks or less) antibiotic treatment be considered following resection arthroplasty for chronic periprosthetic joint infections (PJIs)?

RECOMMENDATION: Yes. Following an aggressive debridement and insertion of an antibiotic-loaded cement spacer (ALCS) or beads, a short-term course of less than two weeks of systemic antibiotic therapy can be considered. Several studies show promising results with infection eradication rates comparable to when a much longer course of antibiotic treatment is used.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 64%, Disagree: 32% Abstain: 4% (Super Majority, Weak Consensus)

RATIONALE

Successful management of PJIs requires appropriate surgical intervention with additional antibiotic therapy. PJIs can be treated by several surgical strategies that range in invasiveness, including debridement and irrigation of the infected prosthesis, one- to two-stage exchange with or without the placement of a spacer or an extension device, resection arthroplasty and amputation. However, the ideal duration of antibiotic therapy, intravenous (IV) alone or combined IV and oral antibiotics, is not known. With increasing concerns about the emergence of antibiotic resistance and the spiraling costs of healthcare worldwide, shorter courses of antibiotic therapy, if equally efficacious to the more traditional 6- to 12-week course, would be a very attractive proposition.

The rationale of using a shortened duration of systemic antibiotics is based on the high local levels of antibiotic that can be achieved following elution from antibiotic-loaded bone cement, whether this is in the form of spacers or cement beads. Local tissue levels of antibiotic are above the minimum inhibitory concentration (MIC) for commonly infecting organisms [1–3] (Tables 1 and 2), and the levels are greater than that which can be achieved with IV administration alone.

Although some groups have reported good clinical outcomes with meticulous debridement and combinations of local and short-term systemic antibiotic therapies, most of the studies examining short-term inter-stage antibiotic treatments were retrospective cohort studies on a small number of patients. There were very few studies in which antibiotic therapy was less than two weeks duration. In addition, there was significant inter-study heterogeneity in the definition of infection, in the treatment approach with regard to the debridement method, in differing combinations of systemic and ALCSs and in the antibiotic therapy after reimplantation. Although the results appear promising, the inter-study heterogeneity makes it difficult to utilize the studies as collective evidence to support short-term inter-stage antibiotic treatment.

In a small randomized controlled trial that did not meet Consort guidelines, Nelson et al. compared inter-stage treatment with antibiotic-laden cement beads, combined with no more than five days of inter-stage systemic antibiotic therapy, to traditional inter-stage systemic antibiotic therapy alone in 26 patients treated for PJIs with two-stage resection arthroplasties. All patients were reimplanted at 6 weeks following stage-I surgery. After a mean follow-up period of 32 months, infection eradication was 100% in the group treated with antibiotic-laden cement beads and 93% in the group treated with systemic antibiotics alone [4].

In a retrospective cohort study, McKenna et al. assessed the effectiveness of a five-day inter-stage course of systemic vancomycin combined with an ALCS containing vancomycin, gentamicin, and tobramycin, following resection arthroplasty for failed total knee arthroplasty (TKA) due to PJIs in 30 consecutive patients. At the gentamicin of reimplantation (mean = 16 days) no infection recurrence was reported. A second five-day course of systemic antibiotics was administered following second-stage reimplantation. At a mean follow-up of 35 months, infection eradication remained at 100% [2].

In a retrospective cohort study, Whittaker et al. assessed a two-week inter-stage course of systemic vancomycin combined with a vancomycin and gentamicin loaded spacer, for hip PJIs. Three patients required a repeat debridement prior to reimplantation due to recurrent infection (7%). Of those patients receiving second-stage reimplantation, 92.7% were infection-free at a mean follow-up of 49 months [5].

Hoad-Reddick et al. reported on a retrospective cohort study that included 38 patients who underwent staged exchange with a combination of ALCS, antibiotic-laden cement (ALC) beads (loaded with vancomycin, gentamicin or both) and broad-spectrum prophylactic systemic antibiotics administered at 8 and 16 hours with no further systemic antibiotics given. Infection eradication after second-stage reimplantation at a mean follow-up of 56.4 months was 89% [6].

In a retrospective cohort study that included 107 patients with hip PJIs (36 of which had recurrent PJIs), Hseih et al. compared outcomes of 56 patients treated with one week of inter-stage IV antibiotic therapy to outcomes of 51 patients treated with 4-6 weeks of IV therapy, followed by two additional weeks of oral antibiotic therapy after reimplantation. Both groups also had antibiotic-impregnated spacers. Infection eradication was achieved in 92.4% (1 week) and 91.3% (4-6 weeks) of patients, respectively at a mean follow-up time of 43 months (range = 24-60 months) [7]. The number of patients in these studies who were infection-free after completing the two-stage procedure ranged from 86.7-100%, comparable to the rates achievable with a standard 4- to 6-week antibiotic regimen.

Appropriate usage of antibiotics is of paramount importance, more so today than ever, in view of emerging antibiotic-resistant organisms. Short-term therapies (i.e., less than two weeks) can be considered when managing patients with PJIs. However, prospective randomized controlled trials are needed to further explore this issue.

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TABLE 1. Therapeutic ranges and minimum biofilm eliminating concentration (MBEC) values for various antibiotics

Antibiotic	Therapeutic Peak (mg/L; µg/mL)	MBEC (mg/L; µg/mL)				
		S. aureus	*MRSA*	*P. aeruginosa*	*S. epidermidis*	*E. coli*
Azithromycin	0.3 - 0.6		5120	2560		
Ceftazidime	< 150			2560 - 5120		
Ciprofloxacin	2.5 - 4		256 - 1280	80 - 1280		
Clindamycin	< 0.5		64 - > 1024			
Colistin	1 - 4			160 - 2560		
Daptomycin	6 - 10	600	1014			
Doxycycline	< 10		64 - 128			
Erythromycin	0.5 - 3	6400	64 - > 1024	2560		
Gentamicin	5 - 10	6400	1 - > 256	512xMIC		
Linezolid	0.5 - 4	6400	4 - > 1024			
Piperacillin	5 - 20			> 5120		
Tobramycin	5 - 10	160 - 4000	≥ 8000	250 - 2000	≥ 8000	62.5 - 125
Vancomycin	25 - 50	2000 - 8000	2000 - 8000		1000 - 8000	

MBEC, minimum biofilm eliminating concentration; MRSA, methicillin-resistant *Staphylococcus aureus*

TABLE 2. Peak local antibiotic concentrations via cement elution

Study	Cement Protocol	Peak Joint Concentrations
Masri et al. [8]	ALCS: 1.2 - 4.8 gm of tobramycin and 1 - 2 gm of vancomycin per 40 gm pack	1.25 - 16.97 mg/L
Hsieh et al. [7]	ALCS: 4 gm vancomycin powder and 4 gm aztreonam per 40 gm pack	vancomycin: 1538 mg/L; aztreonam: 1003.5 mg/L
Anagnostakos et al. [9]	ALCS + beads: 1 gm gentamicin and 4 gm vancomycin per 40 gm pack	gentamicin: 115.70 mg/L; vancomycin: 80.40 mg/L
Fink et al. [10]	ALCS: 'Pre-prepared' mix	gentamicin: 50.93 mg/L; vancomycin: 177.24 mg/L; clindamycin: 322.29 mg/L

ALCS, *antibiotic-laden* cement spacer

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5.11. TREATMENT: ANTIMICROBIAL SUPPRESSION

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QUESTION 1: Is there a role for administration of prolonged oral antibiotics following primary total joint arthroplasty (TJA)?

RECOMMENDATION: No. The administration of prolonged oral antibiotics in the context of perioperative prophylaxis after primary TJA is not recommended. Continuing antibiotic prophylaxis longer than 24 hours after wound closure has not proven to be beneficial; indeed, it may contribute to the development of antimicrobial resistance, carries risks and adds to healthcare costs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 4%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

The use of preoperative systemic intravenous antibiotic prophylaxis reduces the risks of postoperative infections in TJAs. Numerous guidelines, including those developed jointly by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS) and the Society for Healthcare Epidemiology of America (SHEA) [1], all recommend preoperative antibiotic use.

The recent guidelines for the prevention of surgical site infections (SSIs) developed by the Centers for Disease Control and Prevention (CDC) state that in clean and clean-contaminated procedures, no additional antibiotics after wound closure in the operating room are necessary, even in the presence of a drain (Category IA–strong recommendation; high-quality evidence) [2]. The latter recommendation, however, is based on non-orthopaedic procedures. The American Association of Hip and Knee Surgeons (AAHKS) has funded a large randomized prospective study to examine the difference, if any, between a single dose and 24-hour dose of prophylactic antibiotics in patients undergoing TJA. While the results of the latter study are awaited, most surgeons continue to administer multiple doses of prophylactic antibiotics for patients undergoing TJA.

There are, however, numerous studies demonstrating that the use of a short course of antibiotics does not place patients at higher risks of SSIs/periprosthetic joint infections (PJIs) than longer courses of antibiotics [3–5]. A systematic review by Thornley et al. evaluated the evidence for postoperative antibiotic prophylaxis administration and its role for reduction of SSIs among patients undergoing primary total hip or knee arthroplasties [6]. The pooled estimate demonstrated that prolonged postoperative antibiotic prophylaxis did not significantly reduce the rates of SSIs (odds ratio (OR) 0.01, 95% confidence interval (CI), 0.00-0.02). However, the overall quality of the evidence was very low, owing to risk of bias, inconsistency and imprecision in the studies evaluated [6].

There has been minimal work performed that evaluates whether patients undergoing TJA should receive prolonged courses of oral antibiotics. A recent study presented at the annual meeting of AAHKS demonstrated significant reductions in the rates of SSIs/PJIs when prolonged (seven days) or oral antibiotic was administered to patients undergoing TJA. The study was retrospective in nature, consisted of a relatively small cohort, had a short follow-up and did not disclose the exact definition of PJIs or SSIs. Otherwise, there is no other study demonstrating that administration of prolonged oral antibiotics after TJA offers additional benefits to patients. The available evidence does not support continuation of postoperative antibiotic prophylaxis intravenously or orally for the prevention of SSIs in patients undergoing TJA.

There are numerous risks associated with the administration of antibiotics, most important of which is the realistic and sobering issue related to emergence of antimicrobial resistance (AMR). Moreover, the unnecessary use of antibiotics can lead to the development of opportunistic infections, such as *Clostridium difficile* associated diseases, that can result in extended hospital stays, increased costs for episode of care as well as higher morbidity and mortality [7].

In the absence of concrete evidence and due to the dire need for the medical community to observe antibiotic stewardship, we recommend against the prolonged use of oral or intravenous antibiotics in patients undergoing routine primary total hip or knee arthroplasty.

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QUESTION 2: What is the role of oral suppression antibiotics after reimplantation in patients with negative cultures after 14 days of incubation?

RECOMMENDATION: There may be a role for the administration of oral antibiotics to decrease reinfection rates following reimplantation in patients with negative cultures, but further study is necessary.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 73%, Disagree: 21%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

The role of oral antibiotics after two-stage revision was evaluated in one randomized controlled trial [1] as well as three retrospective studies [2–4]. Three of these studies found reduced rates of reinfection in patients who received oral antibiotics following reimplantation. One retrospective study evaluating oral antibiotics in patients with periprosthetic joint infection (PJI) included a subgroup of patients with two-stage revisions and found no differences in implant survival between the suppression and non-suppression cohorts [4]. Follow-up varied in all of the studies, with one study reporting preliminary findings, but still underway. Further more the sample size in all of these studies was relatively small and the longitudinal follow-up duration was limited.

Different antibiotics were utilized in these studies at the discretion of the treating physician, all of which have different bioavailability and antimicrobial spectrum of activity. Some of the antimicrobial therapies chosen to be administered after reimplantation are known to have bioavailability nearing 100% (e.g., fluoroquinolones, linezolid), which is more in the 'active therapy' realm vs. suppressive therapy. The original offending microorganisms also varied substantially, which could affect the results. In one study [3], 50% of the initial cultures at the time of component removal did not identify a microorganism, so these patients were treated empirically, making the choice of agent difficult. Adverse events with oral antibiotics were reported, including patients who discontinued therapy prematurely, and this should always be considered when determining whether antimicrobial therapy is appropriate for a patient.

In essence, these studies may represent a signal that the provision of oral antibiotics after reimplantation may be of benefit; however, there is a definite need to confirm these findings with further study.

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QUESTION 3: Which patients should be considered for administration of long-term suppressive oral antibiotic instead of surgical treatment in patients with chronic periprosthetic joint infections (PJIs)?

RECOMMENDATION: Long-term suppressive oral antibiotics instead of surgical treatment may be considered for patients who are not candidates for surgery, when surgery is not expected to improve the functional outcome for a patient, and for patients who refuse surgery.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 95%, Disagree: 4%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

An extensive literature search was conducted to examine the role of suppressive antibiotics instead of surgical intervention for patients with chronic PJIs. No such study could be identified. To our knowledge, no study has examined specifically the profile of patients who may be considered for long-term suppressive antibiotic treatment instead of surgery for chronic PJIs.

Patients with PJIs are best treated by surgical intervention that includes the removal of infected implants or debridement of the

infected site and exchange of the modular components. The aim of the surgical intervention is to reduce the bacterial load (bioburden) and the biofilm formed on the components that cannot be penetrated by antibiotics or the immune system of the host. In some cases, however, removal of all or part of the infected implants during surgery is not in the best interests of the patient and chronic antibiotic suppression represents, in these circumstances, an unique anti-infective therapy that can be applied to these patients. The administration of antibiotics in this circumstance is meant to minimize the risk of systemic toxicities that the patient may experience as a result of proliferation of the organisms from the infective site. Another reason for administration of antibiotics in this situation is to try to keep the infection at bay by reducing drainage from the wound or the sinus tract [1–6].

The indications for the use of long-term suppressive antibiotics is not well known or well studied in the literature. In the absence of evidence, we believe that suppressive antibiotics instead of surgical intervention may be an option (1) for patients in whom surgery is contraindicated because of the patient's general condition, (2) when surgery is not expected to improve the functional outcome for patient, such as those with multiple prior failures and (3) for patients who refuse surgery.

Given the very low probabilityof obtaining remission of infection, or even control of infection, and the potential adverse effects associated with long-term antibiotics to the patient and the society, this treatment option would be best considered collegially by a multidisciplinary team working together to determine the treatment for the patient.

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Outcomes

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QUESTION 1: What is the definition of success of surgical treatment of a patient with a periprosthetic joint infection (PJI)? What clinical, operative, microbiological and functional metrics should be considered?

RECOMMENDATION: The treatment of PJIs typically does not have a dichotomous outcome. More commonly, the result is a gradient of success or failure. As such, the outcome-reporting tool has been organized into four tiers with each tier encompassing different levels of perceived success or failure. The outcomes reporting for the treatment of PJIs are the following (definitions regarding items within each tier are explained in the rationale section):

Tier 1. Infection control with no continued antibiotic therapy

Tier 2. Infection control with patient on suppressive antibiotic therapy

Tier 3. Need for reoperation and/or revision and/or spacer retention (assigned to subgroups of A, B, C, D, E, and F based on the type of reoperation)

- A. Aseptic revision > 1 year from initiation of PJI treatment
- B. Septic revision (including debridement, antibiotic and implant retention (DAIR)) > 1 year from initiation of PJI treatment (excluding amputation, resection arthroplasty and fusion)
- C. Aseptic revision ≤ 1 year from initiation of PJI treatment
- D. Septic revision (including DAIR) ≤ 1 year from initiation of PJI treatment (excluding amputation, resection arthroplasty, and fusion)
- E. Amputation, resection arthroplasty, or fusion
- F. Retained spacer

Tier 4. Death (assigned to subgroups A or B)

- A. Death ≤ to 1 year from initiation of PJI treatment
- B. Death > 1 year from initiation of PJI treatment

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 82%, Disagree: 14%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

The MusculoSkeletal Infection Society (MSIS) definition for PJIs provided standardization to the patient populations in PJI research [1]. As evidenced by the numerous definitions of success and failure in the literature, the same standardization has not been provided for defining the outcomes for the treatment of PJIs [2–11]. Therefore, a multi-national, multi-institutional and multi-disciplinary workgroup was organized by the MSIS to review the available evidence and propose a gold standard definition in the outcome reporting for the treatment of PJIs to improve the transparency in outcome studies and guide the definition of success for the treatment of PJIs.

Definitions and Considerations

Starting Point of Treatment Assessment

The starting point for the assessment of a treatment can influence the size of the population and alter the reported treatment success. A prior Delphi method definition of success after treatment of PJIs proposed the starting point for assessment does not begin until reimplantation surgery during a two-stage exchange [8]. However, literature on the outcomes of spacers in the treatment of PJI demonstrated that 17% of the patients underwent amputation, resection arthroplasty, arthrodesis or remained with a retained spacer instead of undergoing reimplantation [12]. The starting point for assessing the treatment of PJIs will begin at the time of the initial operation for PJIs, which will be irrigation and debridement, the first stage of a two-stage exchange or following a one-stage exchange.

Infection Control

Because bacterial organisms can undergo internalization by osteoblasts, "infection eradication" may not always be feasible and "infection control" better represents the process of treating PJIs [13]. Since the MSIS criteria for diagnosis of PJIs is simple and well established, the workgroup has defined infection control as a patient not meeting the MSIS criteria for PJIs and not having undergone or in need of further surgery (excluding the planned reimplantation of

a two-stage exchange, a procedure for a complication related to the antibiotic spacer or a planned operation to address soft-tissue issues between two-stages) [14].

Antibiotics

Given the promising results of a recent preliminary study on extended oral antibiotics after the reimplantation of a two-stage exchange, the use of antibiotics beyond the historical treatment period will become extended as more clinicians adopt this approach [15]. The workgroup has defined "off antibiotic therapy" as cessation of antibiotics within 1 year after the initial surgery. Patients are still allowed to be on antibiotics of 10 days or less for a documented infection other than PJI or antibiotics for a pre-procedure prophylaxis (i.e., dental prophylaxis or preoperative antibiotics for another operation).

Reoperation

The reasons for reoperation (excluding the planned reimplantation of a two-stage exchange, a procedure for a complication related to the antibiotic spacer or a planned operation to address soft-tissue issues between two-stages) should be reported as aseptic revisions, septic revisions or amputations, resection arthroplasties or fusions. Any patient undergoing a revision surgery who does not meet the MSIS criteria for PJIs at the time of revision is considered an aseptic revision. Aseptic revision was divided into subgroups with patients revised ≤ year or > one year from the initial surgery in the treatment for PJI. Due to advancements in DNA sequencing demonstrating higher rates of polymicrobial PJI than standard laboratory cultures, assignment of septic revision will apply to any patient revised for infection regardless of the organism [16]. Similar to aseptic revision, subgroups have been assigned based on the duration from surgery. Given some patients continue to live with the spacer, subgroup has been established for patients with a retained spacer.

Minimum Duration of Follow-up

The minimum reporting of any outcome should be 1-year follow-up. When any study reports a minimum follow-up of 1, 5 or 10 years, it will be defined as having short-term, mid-term, or long-term results, respectively.

Death

In the reporting of outcomes in Tier 4, "death" is defined as all-cause mortality with a differentiation between mortality ≤1 year or > 1 year from the initial operation for the treatment of PJIs. As more literature demonstrates the increased risk of mortality for patients undergoing treatment for PJIs, we are gaining a greater appreciation for the effects of PJIs on the host [17–19]. Despite the increased risk of mortality among PJI patients, we still lack the ability to directly or indirectly assign the cause of mortality due to PJIs. Therefore, the workgroup has used all-cause mortality in defining Tier 4.

Appropriate Use of the Outcome Reporting Tool

The system of tiers in the outcome reporting tool is meant to allow for a comprehensive accounting of patients in the treatment of PJIs. Therefore, each patient can only be assigned to a single tier whereby the percentage of patients among all the tiers will amount to a total of 100%. The workgroup suggests all publications reporting on the outcomes of PJI treatment include a table presenting the number of patients assigned to each tier and subgroup with certain tiers. The workgroup has recommended grouping the outcome tiers into three categories as the following: success, failure of secondary causes and failure of PJIs. Patients assigned to Tiers 1 and 2 are considered a successful outcome by representing infection control with no further reoperations. Since not all patients will experience a successful outcome or failure not due to PJIs, Tiers 3B, 3D and 4B are a failure of secondary causes not associated with PJI. Lastly, Tiers 3A, 3C, 3E, 3F and 4A are considered a failure that is directly or indirectly related to PJIs.

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QUESTION 2: Is there a minimum number of periprosthetic joint infection (PJI) procedures that surgeons should perform annually that qualifies them as experts in the management of PJIs?

RECOMMENDATION: While the optimal number of PJI cases a surgeon needs to perform annually to improve outcomes has not been established in the literature, some data suggests that surgeons that care for more PJI patients will have better results than lower volume arthroplasty surgeons. Further studies are needed to identify the minimum number of PJI cases a surgeon should perform to reduce complications and improve outcomes.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 97%, Disagree: 1%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

A recent publication derived from the European Bone Joint Infection Society (EBJIS) reported on a survey based on the annual conference's delegates from all over the world [1]. It was surprising that even in this highly specific group of experts, most of them work in institutions that manage less than 50 PJIs cases per year. In a recent publication from a United Kingdom (UK) Bone Infection Unit (BIU), 362 hip PJIs were reported over a 13-year period, which were treated under the care of 10 consultant (staff) arthroplasty surgeons; this equates to three cases of hip PJI per year per staff member if the workload was evenly spread [2]. Similarly, data from a high-volume UK centre (1,000 total hip arthroplasties (THAs) per year), reported on 131 hip PJIs treated over a 13-year period by 4 surgeon (3 per year) [3]. A recent publication from another European BIU reported on 81 knee PJIs treated over a 1-year period; however, the number of surgeons treating these cases was not included [4]. Lastly, data from a high-volume United States center, reported on 205 hip PJIs over a 13-year period (16 per annum), although the number of surgeons treating the patients was not described [5]. These studies, however, failed to compare the results of higher- and lower-volume PJI surgeons.

A comprehensive systematic review failed to identify any publication that tested a surgeon's case volume as a variable for infection eradication rates or outcomes following PJIs. There are several studies, however, that demostrate that a surgeon's case volume improves outcomes in primary arthroplasty. The arthroplasty literature suggests that in primary hip arthroplasty, 35 cases per year is the optimal number above which complications reduce significantly [6,7]. A significant amount of work investigating the effect of surgeon and hospital volume on outcomes following knee arthroplasty has been performed [8,9]. Both hospital and surgeon volume were associated with decreased morbidity, mortality and length of stay. In a recent study on ouctome following unicompartmental knee arthroplasty (UKA), surgeons performing more than 30 cases per year have a significantly reduced revision rate [10]. The minimum number of cases required for improved outcome in revision work is unknown. Of interest, 80% of surgeons in the UK's national joint registry performing knee revisions undertook 10 or fewer per annum, and similarly 60% of surgeons performing hip revisions undertook ten or fewer per annum [11]. The above observations have led to the development of revision networks in order to 'centralize' the services in the UK in an effort to improve outcomes. Furthermore, data has shown that in addition to volume, the degree to which a surgeon specializes in a specific procedure may be as important as the volume of cases due to factors such as muscle memory, higher attention and faster recall [12,13]. Extrapolating these results to revision arthroplasty for PJIs, we suggest a minimum surgical volume of 25 cases per year for a surgeon to qualify as an expert in PJIs, but further studies are needed to define the optimal number. With only a few retrospective studies identifying an association between surgeon volume and outcomes in primary and revision arthroplasty, we issue a limited recommendation.

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QUESTION 3: What tools (i.e., kidney, liver, index surgery, cemented prosthesis and C-reactive protein (KLIC) score) are available to help predict successful treatment with debridement, antibiotics and implant retention (DAIR)? What is the accuracy of these tools?

RECOMMENDATION: Two prognostic scoring systems have been published and only one has been validated. While several studies exist confirming the significances of the variables utilized by the two scoring systems, the body of literature is heterogeneous and conflicted, such that general statements of their accuracy and applicability cannot be supported.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 91%, Disagree: 7%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Periprosthetic joint infections (PJIs) are some of the most critical and prevalent complications following total joint arthroplasty. PJIs are associated with considerable healthcare expenses as well as patient morbidities and mortalities. Treatment strategies that have been adopted range from conservative management and antibiotic suppression to surgical treatments, such as debridement of the infected joint with or without modular component exchange, single-stage and two-stage revision arthroplasty, arthrodesis and amputation. It is yet to be determined which treatment strategy is the most effective method for treating PJIs in the patient population, but it has been shown that revision arthroplasties following PJIs fare poorly compared to revision arthroplasties following aseptic causes of prosthetic joint failures. Thus, for each patient population, it is important to identify the most appropriate treatment methods in order to prevent the recurrences of infections following treatment of PJIs. DAIR offers the advantage of physically removing most, if not all, of the infected tissue from the periprosthetic space, whereas conservative or arthroscopic treatments are less effective in removing infected tissues. DAIR also does not require the need for reoperation, making it logistically simpler than the two-stage revision arthroplasty procedure. However, indications for DAIR are generally limited to cases of acute postoperative or acute hematogenous infections not yet involving bone or causing implant loosening. There have been several studies reporting the results of DAIR that analyze factors that are predictive for treatment success or failure. However, these studies lack consistency across inclusion criteria, definitions of failure, surgical technique and timing and antibiotic regimens following surgery. This heterogeneity makes it difficult to compare results and is a likely explanation for the markedly varied risk factors and success rates seen following DAIR (16-100%) [1–3].

Two moderate-quality studies sought to construct predictive scoring tools using the most significant identified risk factors to aid in reliably assessing preoperative risk and appropriate patient selection for DAIR. Tornero et al. describes the KLIC-score to predict early failure of DAIR for acute postoperative PJIs in a retrospective regression analysis of 222 procedures (137 knees, 85 hips) [4]. The diagnosis of acute postoperative PJIs was determined using the MusculoSkeletal Infection Society (MSIS) criteria within three months of the index procedure. Early treatment failures were defined as the need for unscheduled surgery, death related to infection within 60 days of DAIR or the need for chronic suppressive antibiotic treatments. Using a logistic regression model, the authors found five independent preoperative predictors of failure. They included chronic renal failure (K- kidney), liver cirrhosis (L- liver), infection of a revision arthroplasty or arthroplasty for femoral neck fracture (I- index surgery) and cemented prosthesis and presenting C-reactive protein > 11.5mg/dL (C- cemented/CRP). The authors assigned each of these factors a point value based on the odds ratio (Table 1) and stratified the risks of failure based on the sum of these risk factors. Patients with a score of 2 or less had a failure rate of 4.5%, while patients with a score of 4 or more had a failure rate of 60%. Those with a score of at least 7 had a 100% rate of failure. Additionally, a score above 3.5 was shown to have an even balance of sensitivity (74%) and specificity (86%) in predicting early failures of DAIR [4].

TABLE 1. Scoring system of independent preoperative predictors of early failure of DAIR for PJI according to the KLIC-score

Abbreviation	Variable	Score
K	Chronic renal failure (kidney), glomerular filtration rate < 30 ml/min	2
L	Liver cirrhosis	1.5
I	Index surgery = revision surgery or indicated for femoral neck fracture	1.5
C	Cemented prosthesis	2
C	C-reactive protein > 11.5 mg/dl	2.5

K, kidney; L, liver; I, index surgery; C, cemented/CRP (reprinted with permission) [4].

The KLIC-score was later validated by Jimenez-Garrido et al. in a cohort of 30 patients with acute postoperative or acute hematogenous PJIs. They concluded that DAIR was likely to successfully treat patients with a preoperative score of < 3.5 and that DAIR was likely to fail and would not be an appropriate treatment for those scoring > 6 [5]. A subsequent external validation study by Lowik et al. retrospectively applied the KLIC-score to 386 hip and knee patients with acute, early PJI [6]. Logistical regressions showed that each point in the KLIC-score corresponds to a 1.32x increase in odds of failure. A score of 3.5 showed the optimal cut-off point for treatment, with a sensitivity of 52% and specificity of 70%. A score higher than 6 points showed a specificity of 97.9%. The KLIC-score exhibited good predictive accuracy with an area under the receiver-operating characteristic curve (0.64), but this was less than what was found in the initial study by Tornero et al. (0.84). The authors attributed this discrepancy to differences between the cohorts and in the regional epidemiology, which highlights the need for local external validation studies prior to widespread clinical adoption [6].

Buller et al. published a nomogram scoring system based on their retrospective regression analysis of 309 hip or knee PJIs treated with DAIR [7]. The authors found that independent predictors of

failure included a longer duration of symptoms of PJI prior to DAIR, elevated erythrocyte sedimentation rate (ESR) at presentation, previous PJIs, previous infections in the same joint and infections caused by *Staphylococcus aureus* (methicillin-resistant and sensitive), vancomycin-resistant *Enterococcus*, methicillin-resistant *S. epidermidis* or coagulase-negative staphylococcal species compared to other causative microorganisms. Those variables plus other patient characteristics, such as Body Mass Index, immunocompromised status, white blood cell count, hemoglobin and whether the hip or the knee is involved are used to calculate a composite score which predicts 1-, 2-, 3-, 4- and 5-year survivals of DAIR [7]. To the investigators' knowledge, this study has not been validated or utilized in subsequent citations.

With respect to the accuracy of these scoring systems, one has been validated in a 30-patient cohort and in an external validation study, but neither has been widely adopted in the literature [5,6]. However, the majority of relevant citations, despite their variability, identified predictive factors that coincide with some of the elements of the KLIC-score and the nomogram. The duration of symptoms of infection prior to DAIR, for instance, was the most widely identify factor associated with treatment outcome, with a longer duration corresponding to increased odds of failure [1,8–15]. In keeping with both systems' scoring methodologies, others have found that elevated inflammatory markers are associated with higher failure rates [8,12,16–18] and DAIR for infected knee arthroplasty has generally less favorable published results compared to their hip counterparts [2,13,19]. Performing DAIR for PJIs of revision arthroplasty [20], arthroplasty for femoral neck fracture [19] or of a cemented prosthesis [21] has also been shown to be predictive of failure in other studies. Other than the KLIC validation studies, there has been one study to identify chronic kidney disease as a predictor of DAIR failure, albeit in a cohort of exclusively gram-negative PJIs treated with DAIR [22]. No other citations, to our knowledge, have correlated liver cirrhosis to DAIR failure.

There are several other associated factors in the literature not captured by the scoring systems. Exchanging the polyethylene or modular components during debridement is consistently described as a predictor of successful treatment [20,23–25] – contemporary publications and reviews conclude that exchange of these should be standard in DAIR based on these results. Postoperative antibiotic treatments greater than 21 days, and more often at least 42 days, have also been described as positive predictors [26–28]. Appropriate antibiotic treatment varies based on causative organisms [22], but multiple citations conclude that the addition of rifampin to the antibiotic regimen is indicated for *S. aureus* infections [16,25,29–32].

The time from index surgery to PJI has had conflicting associations. Some studies show that late (i.e., acute hematogenous) infections have poorer outcomes compared to acute postoperative infections [1,8,13,24,25,33,34], while others show non-inferior results of DAIR for acute hematogenous infections as long as the duration of symptoms is short [15,34,35]. The McPherson host grading classification system, though originally described to predict successful two-stage treatment for PJI, was recently shown in total hip arthroplasty patients to predict success with DAIR [36,37]. McPherson grade A hosts failed at significantly lower rate (8%) compared to grade B (16%) and grade C (44%) hosts [37]. Preoperative anemia (hematocrit < 32.1) was recently shown to predict treatment failure after DAIR (odds ratio 6.7) [38]; anemia was included in the analysis but not found to correlate with failure in the nomogram scoring system by Buller et al. [7].

The majority of relevant citations also describe treatment rates that are pathogen-dependent. Staphylococcal species are overwhelmingly associated with high failure rates, vs. other etiologies [8,39] and most, but not all, show *S. aureus* infections to fail at significantly higher rates than other staphylococcal infections [10,26,28,40–44]. Species and antibiotic sensitivity are generally not clinically available at the time of DAIR using commonly contemporary diagnostic methods, making it impractical to include in a preoperative risk assessment system. It was not included in the KLIC-score, though the citation describes pathogen-dependent results consistent with the literature [4]. It was, however, included in the nomogram, which limits its ability to be adopted as a preoperative tool [7].

Despite the promise of these two reported scoring systems, well-controlled, high-quality studies confirming their accuracy are still lacking. The heterogeneity of the relevant literature supports both scores' methodologies, but not without some degree of conflict or inconsistency. Thus, we conclude that there exist two prognostic scoring systems: one which is a validated, preoperative assessment of risk of early failure for DAIR and one which is a non-validated nomogram of perioperative characteristics predicting 1- through 5-year survivability. Further studies adopting these scores are needed to identify those PJI patients most appropriate for treatment with DAIR.

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QUESTION 4: (A) What is the optimal follow-up plan (i.e., schedule, exam maneuvers, labs, imaging) for patients being treated for periprosthetic joint infections (PJIs)? (B) How frequently should the inflammatory biomarkers be measured after the resection arthroplasty performed as part of two-stage exchange?

RECOMMENDATION:

(A) At present, there is no consensus regarding the optimal follow-up schedule for patients being treated for PJIs and no specific research discussing this topic. In the absence of evidence, we recommend that the patients should be followed at 6 weeks postoperatively, 3 months, 6 months, 12 months, and annually thereafter, with adjustments being made based on individual circumstances. Inflammatory markers should be measured on a weekly basis after resection arthroplasty.

(B) As of now there is no study to assess the frequency with which the biomarkers need to be checked during the course of a two-stage exchange for PJIs. Most of the available studies have checked the available diagnostic battery of the tests, including serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as well as synovial fluid white blood cell (WBC) count, polymorphonuclear (PMN) and leucocyte esterase (LE) at least once prior to the second stage (reimplantation). However, there is no unified protocol that provides recommendations on the timing of these tests. Future studies in this field are required to guide the orthopaedic community and help form a consensus.

LEVEL OF EVIDENCE: (A) Consensus, (B) Consensus

DELEGATE VOTE: Agree: 85%, Disagree: 7%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

The treatment of PJIs includes debridement, antibiotic and implant retention (DAIR) with or without exchange of mobile parts, single-stage exchange, two-stage exchange, long-term antibiotic suppression and salvage procedures (i.e., excision arthroplasty/arthrodesis/amputation) [1]. Due to the unavailability of specific study on this topic, all the papers on PJIs which had contents concerning the follow-up schedule were divided into groups based on specific treatments and reviewed respectively to summarize a relatively ideal follow-up timeline. The overall recommendation for follow-up visits are at 6 weeks, 3 months, 6 months, 12 months postoperatively, and yearly thereafter [2,3]. Zeller et al. [4], in their prospective cohort study on one-stage exchange arthroplasty, and Frank et al., in their multicenter randomized controlled trial that studied the effects of oral antibiotics on the reinfection rates after two-stage exchange, both have implemented the aforementioned follow-up protocol [5].

The follow-up of patients being treated for PJIs needs to be individualized based on their needs and the clinical progress. However, patients with PJIs who have undergone surgical procedures may be at higher risks of complications and issues and hence need to be followed-up more regularly. In addition, part of the clinical progress of these patients is measured using serological inflammatory markers. Thus, more regular follow-up allows the treating orthopaedic team to determine the best course of action. The latter is particularly true for patients who have undergone resection arthroplasty. These patients need to be monitored closely to determine the optimal timing of reimplantation. In addition, these patients need to be seen by the infectious disease specialists to monitor treatment response, and possibly adverse reactions, to the administered antibiotics. Although the inflammatory markers do not exactly determine the timing of reimplantation, it is important that the level of these inflammatory markers declines in the interim stage between resection and reimplantation. Additionally, determining when infection is eradicated and when reimplantation should occur remains relatively unknown which makes recommendations for follow-up also difficult.

Despite the wide array of diagnostic tests that can be used to work up a patient for PJIs, a clinical suspicion is mainly based on the initial history and physical examination [6]. They can not only help to diagnose PJI but also to identify the type of PJI encountered and assess the patient's risk factors as well as the treatment protocols.

The most common physical examinations include evaluation of the appearance of the joint, temperature of the joint skin, swelling, erythema, wound healing issues and pain with range of motion according to a systematic review of the literatures and documents regarding PJIs [6–11]. Acute infections are easier to diagnose due to the typical signs of inflammation including pain, swelling, erythema and warmth of the affected joint, accompanied by impaired wound healing postoperatively. Systemic symptoms such as fever and chills may also occur [11]. However, these typical clinical signs and symptoms may be unreliable or even entirely absent in delayed or chronic infections, especially in slow-growing organisms. The presence of a sinus tract is one of the main diagnostic criteria for PJIs [12]. Persistent pain in the artificial joint with occasional implant loosening or secondary implant failure should be considered as suspicious infections until proven otherwise [13,14].

As of now, there is no study that has specifically investigated the optimal exam maneuvers for patients being assessed for PJIs. However, a prospective study from China was performed to monitor changes in the overlying skin of knees for 12 months following unilateral total knee arthroplasties (TKAs) due to primary osteoarthritis. The authors concluded that different skin temperatures up to 12 months postoperatively may be a normal surgical response and further investigations are required to confirm if increased local skin temperatures are indeed associated with PJI [15].

The majority of studies used a follow-up plan that examines the levels of inflammatory biomarkers, but the frequency of laboratory testing is reported in very few cases. Different schedules consider ESR and CRP monitoring values every week, every two weeks, or every four weeks. However, most of the studies have monitored these biomarkers at least once after antibiotic therapy completion, prior to definitive reimplantation.

According to a study by Ghanem et al. [16], monitoring ESR and CRP before reimplantation can only poorly predict reinfections. This is true when either the absolute value at explantation or the differences between base-line values and those reported at the time of reimplantation are considered. In a study by Hoell et al. [17] they used Interleukin-6 (IL-6) as a biomarker in the follow-up plan. Their study showed that IL-6 levels prior to reimplantation are significantly higher in patients with persistent infection. However, their study was limited by sample size. Serum D-dimer has shown promising results in diagnosing PJIs. Therefore, it was suggested that this test can be used in early diagnosis of acute PJIs and determining the reimplantation timing and infection eradication [18]. However, as mentioned earlier there is no gold standard for diagnosing PJIs, and to confirm or refute the presense of infection, it is highly recommended to use a combination of tests to gather as much information as possible on the systemic response and combine it with physical exam.

Plain X-rays are the primary radiographic tool for assessing prosthetic joints. They are used to detect possible complications, including mechanical loosening, particle disease, component wear, dislocation, fracture, heterotopic ossification and infection. However, X-rays are neither sensitive (only 70%) nor specific (only 50%) [19,20]. It is usually required to compare serial images over a long period of time to be able to properly identify the changes of imaging signs such as radiolucency, osteolysis and migration of implants or spacers. Despite their low sensitivity and specificity in diagnosing PJIs, plain radiographs should be routinely performed to assess patients being treated [10,21,22].

Ultrasound has limited utility for assessing joints and is mostly used to identify the presence of significant local joint effusion [23] and to assist in the joint aspirations. CT scans and MRIs are not the optimal diagnostic tool for patients with prosthetic implants. The presence of metallic implants causes beam hardening and dephasing artifacts. However, both techniques are useful in detecting soft tissue abnormalities, such as joint effusion, sinus tracts, soft tissue abscesses, bone erosions and periprosthetic lucencies.

In terms of positron-emission tomography (PET) scans and other forms of nuclear imaging, further studies are needed because the present data regarding their accuracy is conflicting [24–26].

Bone scans have become less popular, as they have low sensitivity and specificity. The rates can be improved when a dual tracer technique, such as an indium-111-labeled leukocyte scan, is performed simultaneously with a technetium-c99m diphosphonate scan. A systematic review and meta-analysis published in 2016 has investigated the accuracy of imaging techniques in the assessment

of periprosthetic hip infections. The results showed that combined leukocyte and bone marrow scintigraphy was the most specific imaging technique for diagnosing periprosthetic hip infections. Fluorodeoxyglucose PET has an appropriate accuracy in confirming or excluding periprosthetic hip infection, but may not yet be the preferred imaging modality because of its limited availability and relatively higher cost [27].

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QUESTION 5: Is there a benefit for the engagement of a multidisciplinary team for the management of patients with periprosthetic joint infections (PJIs)?

RECOMMENDATION: The treatment of PJIs takes a multidisciplinary approach, with interactions between the orthopaedic surgeon, anesthesiologist, infectious disease specialist, medical microbiologist, plastic surgeon and ancillary service teams. It is demonstrated that centers with experience in the treatment of PJIs, or those adopting standardized protocols, have improved outcomes with lower complications. Until further research demonstrates otherwise, patients with PJIs should be cared for in centers that use a multidisciplinary approach and have experience in the management of PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 98%, Disagree: 1%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Although there are a number of reports on the advantages of multidisciplinary or interdisciplinary teams (MDT/IDT) in prevention of PJIs, there is limited data on its impacts on the outcomes of PJIs. To date, no study has evaluated MDT/IDT interventions in a randomized manner and no meaningful systematic collection of data can be found.

Nevertheless, when PJIs occur, at least in specialist centers in developed countries, a number of medical, surgical and allied health

professionals are involved in management, including orthopaedics, infection disease, microbiology, outpatient parenteral antimicrobial therapy (OPAT), anesthesiology and internal medicine. Furthermore, ancillary services such as nutrition, physical therapy, pharmacy, nursing and care coordination (including physical rehabilitation, counselling, peer support, improved information) are very helpful [1].

The Oxford Bone Infection Unit (OBIU) in England and Oregon Health and Science University (OHSU) in the United States have described models of MDT/IDT care of orthopaedic infections, including PJIs, that have been developed and successfully implemented. Outputs from these centers suggest that MDT/IDT and OPAT services can improve PJI management, not only with regards to diagnosis, treatment and addressing comorbidities, but also with regards to readmissions and overall reduction of hospitalization [2,3].

A small-scale study reported five-year outcomes of a two-stage approach for infected total hip arthroplasties of a single surgeon at a tertiary center. This study prospectively highlighted the vital role of the MDT in managing 125 patients. No patients were lost to follow-up. The authors reported excellent control of infections in a series of complex patients and infections using a two-stage revision protocol supported by a multidisciplinary approach. However, there was an unexplained high rate of mortality in these patients, as 19 patients died during the study period, representing a one-year mortality of 0.8% and an overall mortality of 15.2% at five years [4].

Another study evaluated algorithm-based therapy for patients with PJIs, with emphases on establishing MDT/ IDT discussions and therapy optimizations. The study included 147 consecutive patients (with proven PJIs of the hip or knee) who were treated with a pro forma approach with an average follow-up of 29 months. Patients were treated surgically with either debridement and retention or two-stage exchange (with or without spacer). Interdisciplinary case discussions were held to adjust antibiotic and supportive therapies. The authors then evaluated the infection-free survival of all patients treated and recorded changes in therapy regime and associated complications. Although causative microorganisms were identified in 73.5% of the cases, antibiotic therapy had to be adjusted in 42% of cases based on discussions with infection specialists. A total of 71.4% and 5.4% cases were either definitely or probably free of infection, respectively. Among the study cohort, 3.4% died as a result of PJI and sepsis. Those at risk of treatment failure were cases with a septic or pre-septic status prior to the start of treatment, patients with germs rated as "difficult to treat," or polymicrobial infections, highlighting the importance of an IDT approach and its impact on success in these cases [5].

Furthermore, managing PJIs in the context of biofilms is challenging. The formation of biofilms is highly dependent on numerous factors, including the implant material, the culture media and condition, preconditioning of bacteria, the bacterial species, strain and colony morphologies (e.g., normal, small colony variants, mucoid phenotypes) and the method of evaluation. Studies on animal PJI models differ in animal types and strains, the inoculum size, and the bacterial species and strain. Therefore, animal models may not be generalized to patient management. Clinical PJI studies often lack standardization in antibiotic prophylaxis and information on the time and mechanism of bacterial colonization. Infection caused by virulent or pyogenic bacteria such as *Staphylococcus aureus* induces clinical symptoms much earlier than bacteria with low virulence.

Patients receiving orthopaedic interventions, including arthroplasty, report a negative mental outlook, functional and activity limitations, pain and loss of independence [6]. After a range of hospital admissions, individualized discharge strategies may lower the risks of readmissions and improve patients satisfactions [7]. Past medical history, clinical examination, laboratory investigations, conventional and specialized imaging, joint aspiration, microbiological and histological examinations help diagnose PJIs and are indispensable before planning and providing the appropriate therapy. Differentiation between aseptic and septic prosthetic loosening is difficult. Management of PJIs is expensive, complicated, and has a high morbidity [1]. These patients should have their definitive care by aspecialist MDT/IDT. MDT/IDT management would allow us to determine the extent of unmet needs for patients with PJIs and to evaluate existing support interventions for patients with PJIs and develop appropriate care pathways.

Based on the above search, we believe there is a gap in the available literature for systematic review or conclusion regarding this question. Further systematic studies are needed to determine the design, implementation and evaluation of MDT/IDT in the management of patients undergoing treatment for PJIs.

Literature Search

A literature search from BNI, CINAHL, Embase, HMIC and Medline was performed for ((“multidisciplinary team*” OR interdisciplinary OR MDT) AND ((prosthe* OR arthroplast*)) AND infection*). This search was conducted from inception till 10th January 2018 and 22 articles were found.

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PART III

SHOULDER

Prevention

1.1. PREVENTION: ANTIBIOTICS

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QUESTION 1: What are the optimal perioperative antibiotics for primary shoulder arthroplasty?

RECOMMENDATION: Patients undergoing primary shoulder arthroplasty should receive antibiotics that cover gram-positive and gram-negative organisms specific to the regionally encountered organisms. Peer-reviewed literature supports cefazolin dosing based on body weight (Table 1). Patients with methicillin-resistant *Staphylococcus aureus* (*S. aureus*), or MRSA, colonization should receive weight-adjusted glycopeptide, preferably in combination with cefazolin (Table 1). Patients who are believed to have an intolerance to beta-lactam antibiotics should be further evaluated to determine if they can receive cefazolin. Patients with a true hypersensitivity reaction or adverse reaction that precludes the use of cefazolin should receive vancomycin or clindamycin.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A thorough search of the PubMed database for all available literature on the topic of optimal perioperative antibiotics for primary shoulder arthroplasty was undertaken. There are no prospective controlled studies comparing surgical antibiotic prophylaxis strategies for shoulder arthroplasty that adequately assess clinical outcomes. Studies measuring microbial burden (primarily *Cutibacterium acnes*) at the time of incision after surgical antimicrobial prophylaxis in the setting of shoulder surgery have been disappointing. One small randomized controlled study comparing preoperative doxycycline administration to placebo did not demonstrate a reduction in *Cutibacterium acnes* colonization [1]. The relevance of these findings with respect to surgical prophylaxis in the shoulder is not known. Surgical prophylaxis in total joint arthroplasty does reduce the burden of other cutaneous microorganisms and is recommended for all orthopaedic implant surgery [2–4].

Prophylaxis should target organisms most likely to cause prosthetic shoulder infection. The most common organisms to cause shoulder surgical site infection and periprosthetic joint infection (PJI) are coagulase-negative Staphylococcus species, *Cutibacterium acnes* and *S. aureus* [5–9]. In addition to antimicrobial spectrum, agents selected for prophylaxis should also achieve bactericidal tissue concentration at the time of incision. In the absence of shoulder-specific literature and recognizing the microbiology and other factors we believe it is reasonable to extrapolate from the non-shoulder arthroplasty literature. The agent most likely to provide optimal tissue concentrations for prophylaxis against these organisms is cefazolin, dosed based on patient body weight [10]. Vancomycin should be utilized when patients have a personal history of MRSA colonization or infection. Close attention to dosing based on body-weight and the earlier timing of prophylaxis when vancomycin is utilized is paramount [4,11]. Ideally, vancomycin should not be given alone, however, as studies have identified an increased risk of PJI and surgical site infection potentially due to the narrower spectrum of vancomycin when compared with cefazolin [12,13]. Combination therapy with vancomycin and cefazolin has not been prospectively demonstrated to reduce surgical site infection risk in

TABLE 1. Recommended antimicrobial prophylaxis for patients undergoing primary shoulder arthroplasty

Clinical Situation	Antimicrobial Recommended
No beta-lactam allergy	Cefazolin 2 gm IV (3 gm if patient weighs > 120 kg) starting within 30-60 minutes prior to incision; re-dose Q4 hours; postoperative doses not required and should not be given beyond 24 hours.
Personal history of MRSA infection or colonization	Vancomycin 15 mg/kg (max dose 2 gm) starting within 2 hours prior to incision; postoperative doses not required and should not be given beyond 24 hours. We favor the addition of cefazolin to vancomycin.
Proven, serious beta-lactam allergy	Vancomycin 15 mg/kg (max dose 2 gm) starting within 2 hours prior to incision; postoperative doses not required and should not be given beyond 24 hours.

MRSA, methicillin-resistant *Staphylococcus aureus*

arthroplasty over cefazolin alone, although two studies suggest a trend towards reduced infection [14,15]. Combination therapy may be associated with higher rates of nephrotoxicity than vancomycin alone [14]. However, the value of preventing prosthetic joint infections may still justify its use. Additional study to clarify risks and benefits of these strategies is warranted.

One of the most common causes for use of an alternative perioperative antibiotic other than cefazolin is beta-lactam allergy or intolerance. Most of these patients are not actually allergic and will be able to safely receive cefazolin after evaluation by an allergist [16]. Patients with a true hypersensitivity reaction or adverse reaction that prohibits cefazolin should receive vancomycin or clindamycin in agreement with the Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery [4].

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QUESTION 2: What are the optimal perioperative antibiotics for patients undergoing revision shoulder arthroplasty?

RECOMMENDATION: Patients undergoing revision shoulder arthroplasty should receive prophylactic antibiotics as discussed in Question 1. As addressed in Question 5, if there is suspicion for preexisting infection during surgery, consider oral amoxicillin or first-generation cephalosporin (or oral doxycycline if beta-lactam allergic) until cultures are finalized.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

After a thorough search of the PubMed database for studies evaluating the optimal perioperative antibiotic for patients undergoing revision shoulder arthroplasty, there are no prospective controlled studies comparing surgical antibiotic prophylaxis strategies for revision shoulder arthroplasty that adequately assess clinical outcomes.

Prophylaxis should target organisms most likely to cause prosthetic shoulder infection. The most common organisms to cause shoulder surgical site infection and PJI are coagulase-negative Staphylococcus species, *Cutibacterium acnes* (formerly known as *Proprionibacterium acnes*) and *Staphylococcus aureus* [1–3]. In the setting of revision surgery without an obvious reason for joint failure such as trauma, there may be a question of whether the patient's pain and/or stiffness may be caused by an occult perioperative joint infection (PJI) acquired during a prior case or joint injection. *C. acnes*, in particular, has emerged as a pathogen often cultivated from deep operative specimens in patients undergoing revision for pain and/or stiffness [4].

Unfortunately, inflammatory markers are often normal in these patients, and intraoperative evaluation is often benign-appearing, making it difficult to predict who will ultimately have substantially positive cultures after 14 days of incubation. Thus, surgeons may consider postoperative oral antibiotics to cover the most likely pathogen that may be detected after discharge—*C. acnes*—until cultures are finalized as negative [5]. This is distinctly different from the antibiotic prophylactic strategy for primary shoulder arthroplasty cases, which usually stops when the case concludes, certainly within 24

TABLE 1. Recommended antimicrobial prophylaxis for patients undergoing revision shoulder arthroplasty

Clinical Situation	Antimicrobial Recommended at Surgery (Note: Administer on time as usual, even if concerned about occult infection.)	Postoperative Antimicrobials to Consider if High Intraoperative Suspicion of Infection
No beta-lactam allergy	Cefazolin 2 gm IV (3 gm if patient weighs > 120 kg) starting within 30 minutes prior to incision; re-dose Q 4 hours; postoperative doses not required and should not be given beyond 24 hours.	Amoxicillin 500 mg PO Q 8 H or cefadroxil 500 mg PO BID x 14 days until operative cultures are reported negative. (Adjust for renal insufficiency.)
Personal history of MRSA infection or colonization	In **addition** to cefazolin above, add vancomycin 15 mg/kg (max dose 2 gm) starting within 1 hour prior to incision; postoperative doses are not required and should not be given beyond 24 hours.	Same as above, unless positive intraoperative gram stain or culture positive for MRSA (in which case, convert to treatment program with ID consultation).
Proven, serious beta-lactam allergy	Vancomycin 15 mg/kg (max dose 2 gm) starting within 1 hour prior to incision; postoperative doses are not required and should not be given beyond 24 hours.	Doxycycline 100 mg PO Q 12 H x 14 days until operative cultures are reported negative.

BID, twice daily; MRSA, methicillin-resistant *Staphylococcus aureus*; PO, orally; Q H., every hour

hours post-operatively [6]. Continuing antibiotics postoperatively carries risk of adverse events such as diarrhea, *C. difficile* infection, other side effects, toxicities, development of resistance and drug interactions.

In addition to antimicrobial spectrum, agents selected for prophylaxis should also achieve bactericidal tissue concentration at the time of incision. In the absence of shoulder-specific literature and recognizing the microbiology and other factors, we believe it is reasonable to extrapolate from the non-shoulder arthroplasty literature. The agent most likely to provide optimal tissue concentrations for prophylaxis against these organisms is cefazolin; with dosing based on patient body weight. Vancomycin can be added when patients have a personal history of MRSA colonization or infection, but, ideally, vancomycin should not be given alone. Studies have identified an increased risk of periprosthetic joint infection and surgical site infection, when prophylaxis with an agent other than cefazolin is used [7,8]. One of the most common causes for use of an alternative perioperative antibiotic other than cefazolin is a beta-lactam allergy or intolerance. Most of these patients are not actually allergic and will be able to safely receive cefazolin after evaluation by an allergist or the administration of a test-dose if the prior reaction was felt to be mild. Patients with a true hypersensitivity reaction or adverse reaction that prohibits cefazolin should receive vancomycin or clindamycin in agreement with the Clinical Practice Guidelines for Antimicrobial Prophylaxis in Surgery [9].

Of note, timely administration of intravenous prophylactic antibiotics immediately before incision is unlikely to negatively impact the yield of deep cultures, if they are obtained [10].

Studies measuring microbial burden (primarily *C. acnes*) at the time of incision after surgical antimicrobial prophylaxis in the setting of shoulder surgery have been disappointing [11,12]. One small randomized controlled study comparing preoperative doxycycline administration to placebo did not demonstrate a reduction in *C. acnes* colonization [13]. The relevance of these findings with respect to surgical prophylaxis in the shoulder is not known. Surgical prophylaxis in total joint arthroplasty does reduce the burden of other cutaneous microorganisms and is recommended for all orthopaedic implant surgery [14].

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QUESTION 3: Are there perioperative antibiotics that should be used for patients who have specific preoperative risk factors (e.g., patient sex and comorbidities) for shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: While risk of infection may be affected by demographics and comorbidities, outside of known methicillin-resistant *Staphylococcus aureus* (MRSA) colonization or true allergy, there are not patient-specific factors that justify a change in prophylaxis recommendations. Patients with MRSA colonization should receive a glycopeptide in addition to standard prophylaxis.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The most common organisms to cause shoulder PJI are coagulase-negative staphylococcus species, *Cutibacterium acnes* and *Staphylococcus aureus* [1–7]. While the risk of shoulder PJI is impacted by comorbidities, and the prevalence of *Cutibacterium acnes* colonization is higher in men, there is no available data to support targeted modification of antimicrobial prophylaxis outside of the setting of known MRSA colonization. In the hip and knee arthroplasty setting, one study did not find that differential antimicrobial prophylaxis impacted surgical site infection risk when comorbidities were considered [8]. Studies have identified an increased risk of hip and knee PJI and surgical site infection when prophylaxis with an agent other than cefazolin is used [9,10].

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QUESTION 4: What is the optimal duration of perioperative antibiotics following primary or revision shoulder arthroplasty?

RECOMMENDATION: For primary shoulder arthroplasty, prophylactic intravenous (IV) antibiotics should be given within one hour prior to incision to decrease the risk of infection. Intravenous antibiotics may be continued for 24 hours postoperatively. For revision shoulder arthroplasty, intravenous antibiotics should be given within one hour prior to incision. While controversial, the current evidence suggests that prophylactic antibiotics should not be routinely held until tissue for culture is obtained (see Section 2.5. Diagnosis: Sampling, Question 7). Intravenous antibiotics should only be continued for 24 hours postoperatively, unless there is a concern for periprosthetic infection. Antibiotics can be continued up until final culture results are obtained in revision cases if there is some suspicion of infection while awaiting the final culture results.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Primary Shoulder Arthroplasty

Prophylactic IV antibiotics should be started within one hour prior to incision to decrease the risk of infection [1–7]. IV antibiotics may be continued for 24 hours postoperatively [5–7].

However, recent recommendations from the Center for Disease Control and Prevention (CDC) suggest that prophylactic antibiotics should be administered such that a bactericidal concentration is present in the serum and tissues prior to incision and additional prophylactic antibiotic treatment should not be administered after the surgical incision is closed for clean and clean-contaminated procedures even in the presence of a drain [8]. Similar recommendations have recently been proposed by the World Health Organization advocating preoperative antibiotic prophylaxis without postoperative dosing [9].

Revision Shoulder Arthroplasty

IV antibiotics should be started within one hour prior to incision. There remains some controversy regarding whether or not to administer antibiotics prior to obtaining cultures in the revision setting. Based upon previous experience with revision shoulder arthroplasty [10], McGoldrick et al. recommended withholding prophylactic antibiotics until after tissue cultures have been obtained especially in cases "that have no overt preoperative evidence of clinical infection"[11]. Nevertheless, there is some evidence suggesting that withholding prophylactic IV antibiotics prior to revision for obvious or highly suspected infection is not needed, but this is mostly reported from the hip and knee arthroplasty literature [12,13]. Routine prophylactic IV antibiotics should only be continued for 24 hours postoperatively, unless there is a concern for periprosthetic infection in which case IV or oral antibiotics can be continued for up to 3 weeks postoperatively while awaiting the final culture results [12,14,15]. *C. acnes* may require 13-17 days to grow, necessitating antibiotics for 2 weeks following revision arthroplasty with a concern for periprosthetic joint infection [11,14–18].

Re-dosing of prophylactic antibiotics has been recommended for procedures lasting longer than 3-4 hours [19,20], although there are no shoulder arthroplasty studies on re-dosing of antibiotics.

Note: Despite appropriate skin prep and preoperative IV antibiotics, *C. acnes* can still be grown from the native tissue of the shoulder including within the glenohumeral joint in patients without prior surgery [17,21,22].

Shoulder Surgery Articles: 9 Studies
0 – Level I studies
0 – Prognostic Level II studies
4 – Retrospective Cohort Level III studies
3 – Case Series Level IV studies
2 – Level V opinion

TKA/THA/Other Surgical Articles: 12 Studies
1 – Level I studies
1 – Prognostic Level II studies
4 – Retrospective Cohort Level III studies
3 – Case Series Level IV studies
3 – Level V opinion

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Authors: Trisha Peel, Edward Yian, Surena Namdari

QUESTION 5: Is there a role for postoperative (pending culture results) antibiotics after revision shoulder arthroplasty without suspicion for infection?

RECOMMENDATION: In revision shoulder arthroplasty without clinical suspicion for infection, prolonged antibiotics are not routinely required.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The prevalence of subclinical infections (unexpected positive culture (UPC)) is especially common with shoulder arthroplasty due to anatomic and demographic factors. The rate of positive cultures in primary and revision arthroplasty settings have been reported as high as 56% [1–3]. However, the significance and optimal treatment for UPCs remains unknown. There is limited data in the shoulder literature for or against any role for postoperative prophylactic/suppressive antibiotics after revision shoulder arthroplasty without clinical or radiographic signs of infection. While several studies described the use of prophylactic or suppressive antibiotics after revision shoulder arthroplasty, there was a lack of prospective randomized studies and none of the studies specifically evaluated their efficacy or included a comparative group.

Among published studies for outcomes specifically after revision shoulder arthroplasty with unexpected positive cultures, all were retrospective studies with differing and suboptimal methodologies [4–8]. None of the studies found a detrimental effect associated with not prescribing prolonged antibiotics postoperatively, although one study with no comparison group reported a 25% recurrence rate after UPC. For those studies that treated UPC with prolonged antibiotics, recurrence rates were low (0-3.5%). One systematic review confirmed a pooled true infection rate after UPC of 10.2% with antibiotic use not influencing the rate of occurrence of true infection after UPCs ($p = 0.498$) [9]. In the lower extremity arthroplasty literature, there was one randomized controlled study which found a limited benefit to prolonged oral antibiotic therapy after two-stage revision with negative cultures (5% versus 19%), although culture profiles from the reinfection tended to differ from the original infection organism profile [10].

One study used antibiotic cement and 24 hours of routine postoperative antibiotics with 1 superficial infection and no deep infections after revision shoulder arthroplasty [4]. Another study reported at least a 10% persistent infection rate after one-stage shoulder arthroplasty revision although antibiotic use and positive cultures did not influence the rate of true infections [5]. Another study reported a 23.9% UPC rate after revision shoulder arthroplasty with standardized UPC treatment of 6 weeks antibiotics or 2 weeks antibiotics at surgeon discretion. They found only 1 recurrent infection in the UPC group, 3.5% versus 3.4% in the non-UPC group [6]. Another study reported 8/28 (29%) UPC rate after revision shoulder arthroplasty and only treated one with antibiotics postoperatively for 4 weeks (due to superficial wound infection). Of 8 patients, 2 (25%) developed late clinical infection with *C. acnes* [7]. The last study reported a 49% positive culture rate after revision shoulder arthroplasty and treated patients based on a protocol of 6 weeks intravenous (IV) and 6 months of oral antibiotics if > 2 cultures were positive. No patients (0%) had recurrence of infection with this protocol for the positive culture group and negative culture groups [8]. Two studies reported a 19-42% complication side-effect rate from prolonged antibiotic use which was seen in both oral and IV medication use [4,8]. The vast majority (> 80%) of UPCs were *C. acnes* or Coagulase-negative *Staphlococcus* organisms and, therefore, meaningful comparisons to other more virulent organisms could not be performed.

Recent recommendations from the World Health Organization and the Centers for Disease Control and Prevention suggest a single perioperative dose is adequate for clean and clean-contaminated procedures [11,12]. One meta-analysis included 69 randomized controlled trials and did not demonstrate a difference in the odds of surgical site infection with a single intraoperative dose compared to multiple doses of postoperative surgical antimicrobial prophylaxis (odds ratio (OR) 0.89; 95% confidence interval (CI) 0.77–1.03) [12]. Encompassing concerns regarding the potential adverse consequences of antimicrobial use, in particular the risk of antimicrobial resistance, the panel made a strong recommendation, based on moderate quality evidence, that surgical antimicrobial prophylaxis should not be extended beyond the completion of the operation [12]. The applicability to unexpected positive cultures was not addressed in the studies.

In aggregate, these retrospective studies show no supporting evidence for routine use of prolonged antibiotic use over no prolonged antibiotic treatment in the setting of UPC after revision shoulder arthroplasty. Specifically, there is no identified evidence to demonstrate earlier preemptive treatment of UPC will ultimately alter outcomes. Patients without true infection may be unnecessarily exposed to a significant course of prolonged antimicrobials. There are well-reported risks of antibiotic-related side-effects and less obvious risks of antibiotic resistance with widespread prescribing. Additionally, there is no supporting evidence that suggests that antibiotic treatment should differ between UPC organisms.

A comprehensive literature review was performed to identify all studies on prophylactic/suppressive antibiotics after revision shoulder arthroplasty. Searches for the terms “shoulder replacement,” “infection,” “antibiotics,” “postoperative” and “joint replacement” were performed using the search engines PubMed and Google Scholar, which were searched through February 2018. Inclusion criteria for our systematic review were all English studies (Level I-IV evidence) that reported on antibiotic prophylaxis, or lack thereof, in cases of revision shoulder arthroplasty. Exclusion criteria were non-English language articles, nonhuman studies, retracted papers, case reports, review papers, studies with less than < 10 patients in the sample size, studies without clinical follow-up/infection rates and technique papers without patient data. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed. Thirty articles met inclusion and exclusion criteria and were reviewed.

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1.2. PREVENTION: INTRAOPERATIVE

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QUESTION 1: Should antibiotic-impregnated cement be used during shoulder arthroplasty (primary and revision)?

RECOMMENDATION: There is insufficient evidence to determine whether antibiotic-impregnated cement should be used during primary or revision shoulder arthroplasty.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive review was performed to identify studies relating to the use of antibiotic impregnated cement in primary and revision shoulder arthroplasty. Searches for the terms "shoulder replacement," "shoulder arthroplasty," "prosthesis infection" and "postoperative infection" were undertaken using the search engines PubMed, Embase and Medline. Inclusion criteria included all systematic reviews, randomized controlled trials, cohort studies, case-controlled studies and case series with more than three patients with periprosthetic shoulder infections. Exclusion criteria consisted of case reports, case series with three or fewer patients with shoulder periprosthetic infection, expert opinions, articles relating to periprosthetic infections of joints other than the shoulder and publications not published in the English literature.

Periprosthetic joint infection (PJI) is relatively rare in shoulder arthroplasty (0.4–2.9%) but can be significantly higher in reverse shoulder arthroplasty [1]. PJI can have devastating implications for the patient and lead to significant cost and care provision challenges to the treating surgical teams. Minimizing the risk of infection is, therefore, imperative and optimization of cement fixation with the use of antibiotic-impregnated cement has been proposed as one such method [2]. Indeed, its use has long been suggested as an effective means of reducing the risk of lower limb arthroplasty infection [3].

In cemented primary shoulder arthroplasty, the choice of cement may be influential in the prevention of prosthetic joint infection. However, there is little reported in the literature on the effects of cement choice. Nowinski et al. [2] authored the only shoulder-specific publication in our literature review in which a primary reverse shoulder arthroplasty was cemented using either antibiotic loaded or plain cement. However, it was a retrospective study of 501 implants, divided into two groups (265 vs. 236), with four surgeons using three different antibiotic and cement combinations for differing primary pathologies. Deep infection was noted in 3% of the plain cement group, but none were reported in the antibiotic cement group. This was statistically significant ($p < 0.001$). However, there is a significant selection bias relating to these groups of patients as they were treated in different facilities by different surgeons, and there is, therefore, a substantial risk of confounding variables. In particular, the group without antibiotic-impregnated cement had over twice as many diagnoses of post-traumatic arthritis ($n = 37$) compared to the group in which antibiotics were used ($n = 16$). There were no cases of humeral loosening or osteolysis in the group with antibiotic-impregnated cement.

In revision shoulder arthroplasty, the revision procedure is often dictated by the cause of failure and the underlying pathology. There is no evidence regarding the use of antibiotic impregnated

cement in managing aseptic loosening with a one-stage prosthesis exchange. However, in the management of PJI, the role of antibiotic loaded cement choice may be dependent upon the type of operative revision: debridement and implant retention, one-stage revision, two-stage revision and resection arthroplasty.

Two publications [4,5] do report a series in which no recurrence of infection was noted following the use of antibiotic impregnated cement during one-stage revision of infected shoulder arthroplasty; however, the sample sizes were small with 16 patients in one cohort and 32 in the other. There was no comparative control group using plain cement, and, as all patients also underwent debridement and postoperative antibiotic therapy, no firm conclusions can be drawn regarding the independent relevance of the cement due to the presence of multiple confounding variables.

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QUESTION 2: What is the role of topical intrawound antiseptics (dilute betadine lavage, acetic acid or antibiotics added to the irrigation solution) and antibiotic powder (such as vancomycin) during primary or revision shoulder arthroplasty?

RECOMMENDATION: Dilute povidone-iodine and/or vancomycin powder may have a role in patients considered at high-risk for periprosthetic joint infection (PJI) after primary or revision shoulder arthroplasty based on data extrapolated from other orthopaedic specialties.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

There is no data in the shoulder literature specific to the use of specific intrawound antiseptic agents, irrigation solutions or antibiotic powders. Because of this, expert recommendations will have to be inferred from data from spine surgery [1,2], elbow surgery [3] and lower extremity arthroplasty [4]. There are two randomized single-blinded studies that demonstrated the efficacy and safety of dilute betadine irrigation at reducing the risk of infection in spinal surgery [5,6]. Based on a review of this literature, there appear to be advantages associated with the utilization of dilute betadine and vancomycin powder in cases of primary surgery for prevention of surgical site infection and in cases of PJI treatment for prevention of recurrent PJI. However, the data does not consider the risks of development of antimicrobial resistance with use of vancomycin powder. Betadine may have a negative influence on osteoblast proliferation in vitro [7], and so utilization in cases of fracture may not be recommended. While data is lacking specifically for the shoulder, consensus from the hip/knee, trauma and spine groups provide the ability to make some generalized recommendations for primary and revision shoulder surgery.

TABLE 1. Characteristics of studies assessing intrawound agents, irrigation solutions or antiobiotic powders*

Study	Methods	Intrawound Product/Joint	Site	Result
Yan et al. [3]	Retrospective	Vancomycin powder	Elbow	Positive result: 6.4% SSI vs. 0% infection SSI
Riesgo et al. [4]	Retrospective	Dilute povidone-iodine lavage plus vancomycin powder	Lower extremity PJI	Positive result: 16.7% failed vs. 37% failed
Hey et al. [1]	Retrospective cohort comparative	Vancomycin powder	Spine	Positive result: 0.9% SSI vs. 6.3% SSI
Ghobrial et al. [2]	Meta-analysis	Vancomycin powder	Spine	Systematic review: confirms safety
Tomov et al. [8]	Retrospective	Vancomycin powder, betadine	Spine	Positive result: SSI rates were reduced by 50%

* None of these studies evaluated the shoulder specifically. SSI, surgical site infection; PJI, periprosthetic joint infection

A comprehensive literature review was performed to identify all studies examining the use of intrawound antiseptics and antibiotic powder in shoulder arthroplasty. Searches for the terms "intrawound antiseptics shoulder" (0/0), "antibiotic powder shoulder" (3/0), "betadine shoulder" (8/0), "irrigation solution shoulder" (18/1) and "shoulder irrigation infection" (81/0) were performed using the search engines PubMed and Scopus, which were searched through February 2018. Inclusion criteria for our systematic review were all English language studies (Level I-IV evidence) that reported on use of intrawound antiseptics or antibiotic powder in primary or revision shoulder surgery. Exclusion criteria were non-English language articles, nonhuman studies, retracted papers, case reports, review papers, studies with less than 10 patients in the sample size, studies without clinical follow-up/infection rates and technique papers without patient data. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed. We identified zero articles from PubMed and zero articles from Scopus that met all criteria. Given the limited number of articles identified with the search terms used, searches were separately performed to identify studies on intrawound antiseptic and antibiotics powder outside of the shoulder literature.

Of note, the Centers for Disease Control and Prevention released a recommendation on the use of vancomycin in 1995. Due to concerns for development of antimicrobial resistance, routine utilization of vancomycin in prophylaxis has been discouraged. Instead, use of vancomycin is believed to be acceptable for "prophylaxis for major surgical procedures involving implantation of prosthetic materials or devices at institutions that have a high rate of infections caused by methicillin-resistant *Staphylococcus aureus* or methicillin-resistant *S. epidermidis*. A single dose of vancomycin administered immediately before surgery is sufficient unless the procedure lasts greater than six hours, in which case the dose should be repeated. Prophylaxis should be discontinued after a maximum of two doses." This position statement has not been updated recently or amended to include a discussion of vancomycin powder.

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Authors: Jim Kelly, Vani Sabesan, Diego Lima, Michael Rozell

QUESTION 3: Do surgical drains influence the risk of infection in patients undergoing primary or revision shoulder arthroplasty?

RECOMMENDATION: There is no evidence to support routine use of closed-suction drains in patients undergoing shoulder arthroplasty for the prevention of periprosthetic joint infection (PJI).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

We conducted literature search of PubMed for all articles published on closed surgical drains after anatomic total shoulder arthroplasty (TSA) and reverse total shoulder arthroplasty (RTSA) in the primary and revision settings. The exact search queries performed included the following keywords: "surgical drain in shoulder arthroplasty" in Medical Subject Headings (MeSH) Terms, "closed wound drainage in shoulder arthroplasty," "surgical wound drainage in shoulder arthroplasty" on Title/Abstract and in combination. The initial search produced five articles, including both shoulder and elbow arthroplasty, but after reviewing the elbow arthroplasty-related studies, all of these deemed to not provide information relevant for the purposes of this review and were excluded. This left two articles, both of which had their entire manuscripts analyzed thoroughly for relevance and inclusion.

There is a paucity of literature regarding the use of postoperative closed-suction drains and the relationship to infection and PJI after shoulder arthroplasty [1].

There are no current American Academy of Orthopaedic Surgeon (AAOS) clinical practice guidelines (CPG) which comment on the use of a postoperative drain following TSA or RTSA. While very limited literature is available regarding postoperative drain use in TSA or RTSA, there are several studies that have evaluated blood loss, change in hemoglobin, clinical outcomes and complication rates related to the use of drains after total knee arthroplasty (TKA) and total hip arthroplasty (THA) [1].

A level III, case-control study compared 64 patients who underwent TSH and RTSA without the use of a closed-suction drain to 304 patients that had a drain placed. This study found that drain usage was associated with lower postoperative hemoglobin, longer length of stay and lower postoperative simple shoulder test scores [1]. There was no clinically significant difference in the transfusion rates, superficial wound infections or deep infections. As is sometimes reported in the parallel TKA and THA literature evaluating closed suction drainage, there was no mention of hematoma

formation or analgesic requirements when comparing patients with and without drain use [1].

In 2007, a Cochrane Database Systematic Review evaluated 36 studies regarding the use of closed suction surgical wound drainage after orthopaedic surgery and reported only one study specific to shoulder surgeries by Gartsman et al. [2]. This level II, randomized trial evaluated length of hospital stay, wound dehiscence, infection, reoperation rates and hematomas in patients undergoing TSA, hemiarthroplasty, rotator cuff repair and anterior shoulder instability surgery and found no differences between patients who did or did not receive a drain [3].

Overall, there are few available studies, and these are not sufficiently powered to detect a difference in infection rates after shoulder arthroplasty.

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QUESTION 4: What is the role of tranexamic acid (TXA) during primary or revision shoulder arthroplasty (SA) in decreasing the risk of periprosthetic joint infection (PJI)?

RECOMMENDATION: There is no evidence to support routine use of TXA in patients undergoing shoulder arthroplasty for the prophylaxis of PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Patients undergoing SA may experience variable degrees of perioperative bleeding and blood loss, which in the most severe cases, may result in complications including hematoma formation [1], acute symptomatic anemia and the need for blood transfusions [2–4]. It has been suggested that there is an association between blood transfusion and wound hematomas with postoperative morbidity, including periprosthetic infection [5,6]. While hematomas requiring surgery are uncommon with a reported rate of 0.3% [5], blood transfusions are more common with a reported rate of 4.3% to 6.7%. [3,4,7,8] Besides the costs, allogeneic blood transfusion is associated with rare but serious complications, including allergic and immune-mediated reactions, hemodynamic overload and risk of blood borne infections [9]. In addition, allogeneic blood transfusions may have an immunomodulatory effect [10] that may predispose to increased risk of periprosthetic infection rate, as seen in total hip or total knee arthroplasty [11] as well as in SA [6].

TXA is a synthetic anti-fibrinolytic agent that has been shown to be a successful and cost-effective agent for reducing blood loss and transfusion requirements for patients undergoing total hip arthroplasty (THA) and total knee arthroplasty (TKA) [12]. Two recent meta-analyses [13,14] of TXA use in patients undergoing primary SA found that TXA is an effective intervention to decrease blood loss as measured by drain output, change in hemoglobin (Hb) and total calculated blood loss. Nevertheless, the effectiveness of TXA in reducing transfusion rates after SA has been conflicting. One meta-analysis reported a benefit of TXA [14] in reducing blood transfusion while a second reported no differences in the transfusion rate when TXA was used perioperatively [13]. Possible reasons for conflicting results are (1) the inclusion of non-randomized studies with biased methodology, (2) a high rate of included studies with zero events of transfusion that were excluded from the calculation of the pooling effect and (3) when there are findings that are not conclusive, there is a lack of an additional analysis to further determine the conclusiveness of the results given the low rate of events. As a result, in order to evaluate the effectiveness of TXA to reduce transfusion rates, we performed a new systematic review and meta-analysis that included only randomized controlled trials (RCT), which compared the use of TXA compared to placebo in patients undergoing SA. This meta-analysis considered the primary outcomes to be the effect of TXA upon transfusion rates, formation of hematomas and thromboembolic events. Secondary outcomes included blood loss as measured by drain output, change of Hb and calculated total blood loss.

Methods

The methodology described in the Cochrane Handbook for Systematic Reviews of Interventions [15] was followed to conduct this review and was reported in accordance to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [16]. Cochrane Central Register of Controlled Trials, Embase and Medline were searched up to March 15, 2018. Four RCTs [17–20] involving 375 patients undergoing primary SA were included. The risk of bias of the included studies was assessed and the pooled risk estimates were calculated with random-effect models. For the primary outcomes (transfusion rate and thromboembolic complications), as most of the trials had no events in the tranexamic acid or control group (zero-event studies), a 0.5 continuity correction was used to include data from those RCTs [21]. A trial sequence analysis was conducted to assist in the interpretation of the conclusiveness of the meta-analysis for the effect of TXA in the risk of blood transfusions. The quality of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach.

Results

This meta-analysis confirmed previous meta-analysis results and found that TXA is associated with significantly lower perioperative blood loss compared with placebo and that there is no higher risk of thromboembolic events with TXA (Table 1). However, this meta-analysis found that there was no significant difference for the risk of

TABLE 1. Summary of findings

Outcome No. of Participants (Studies)	Relative Effect (95% CI)	Anticipated Absolute Effects (95% CI)			Certainty
		Without TXA	With TXA	Difference	
Rate of blood transfusion (Transfusion) assessed with: Number of patients who received a postoperative transfusion of packed red blood cells No. of participants: 375 (4 RCTs)	**RR 0.53** (0.17 to 1.64)	**Study population**			⊕⊕ O O LOW [a,b]
		3.7%	**2.0%** (0.6% to 6.1%)	**1.8% fewer** (3.1% fewer to 2.4% more)	
		Low-risk transfusion patients*			
		1.0%	**0.5%** (0.2% to 1.6%)	**0.5% fewer** (0.8% fewer to 0.6% more)	
		High-risk transfusion patients*			
		15.0%	**8.0%** (2.6% to 24.6%)	**7.0% fewer** (12.4% fewer to 9.6% more)	
Thromboembolic complications (TEC) assessed with: Number of patients that developed a thromboembolic complication during follow-up (DVT, PE, Stroke) No. of participants: 375 (4 RCTs)	**RR 0.70** (0.11 to 4.38)	0.5%	**0.4%** (0.1% to 2.3%)	**0.2% fewer** (0.5% fewer to 1.8% more)	⊕⊕⊕O MODERATE
Total blood loss (TBL) assessed with: Estimation of total blood loss with Good's and Nadler's formula No. of participants: 264 (3 RCTs)	-	The mean total blood loss was **1344** ml	-	MD **279.5 ml lower** (411.7 ml lower to 147.3 ml lower)	⊕⊕⊕⊕ HIGH
Postoperative blood loss (PBL) assessed with: Drain output in milliliters (first 24 hours) follow up: mean 1 days No. of participants: 267 (3 RCTs)	-	The mean postoperative blood loss was **216** ml	-	MD **105.4 ml lower** (161.4 ml lower to 49.4 ml lower)	⊕⊕⊕⊕ HIGH
Decrease in hemoglobin (Hemoglobin change) assessed with: Change of preoperative versus lower postoperative hemoglobin (g/dL) No. of participants: 267 (3 RCTs)	-	The mean decrease in hemoglobin was **3.32** g/dL	-	MD **0.7 g/dL lower** (1 g/dL lower to 0.39 g/dL lower)	⊕⊕⊕⊕ HIGH

CI, confidence interval; RCT, randomized control trials; TXA, tranexamic acid

* These numbers were estimated from the literature, considering the rate of transfusion along with a low and high risk of transfusion.

a. The confidence interval crosses the clinical decision threshold between recommending and not recommending tranexamic acid (RR=1 meaning no difference in the rate of transfusion between tranexamic acid and placebo).

b. The accrued sample size of the meta-analysis is underpowered. The estimated optimal sample size with an alpha error of 5%, 80% of power and RRR of 57.4% with a basal risk of 3.7%, was 1555 patients.

Hematoma formation was assessed as an outcome, but it was not included in this table as there were only one trial that reported results.

blood transfusion after SA when comparing TXA with placebo (risk rate 0.53, 95% confidence interval 0.17 to 1.64). Due to the fact that the rate of transfusion after SA is low, the current data is too sparse to provide conclusive evidence for the effect of TXA on blood transfusions. In addition, there is insufficient evidence for the effect of TXA upon hematoma formation or other clinical outcomes after SA.

Conclusion

While this meta-analysis confirmed the effect of TXA in decreasing blood loss, the evidence for its effects on direct clinically important outcomes like rate of transfusions or hematoma formation was inconclusive. Blood loss is a surrogate outcome and there are no defined thresholds to associate a determined amount of blood loss to those clinically important outcomes.

The use of TXA in patients at high risk for transfusion or patients undergoing complex revision arthroplasty has not been adequately studied. Patients at high risk for transfusions include those with low preoperative Hb and hematocrit levels (Hb < 13 g/dL and hematocrit < 39.6%) [3,7,8,22,23], operative time longer than 5 hours [24], surgery with a diagnosis of posttraumatic or rheumatoid arthritis [2,3], and patients with diabetes or ischemic heart disease [8,24]. The use of TXA in these at-risk populations might be justified given the higher baseline risk of transfusion and the greater impact of blood loss. However, this is a recommendation that is weak and limited by the lack of direct evidence. Further study of TXA in these higher risk patients is warranted.

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1.3. PREVENTION: PATIENT CHARACTERISTICS

Authors: Brent Morris, Joseph J. King

QUESTION 1: What is the role of medical comorbidities as potential risk factors for periprosthetic joint infection (PJI) following primary or revision total shoulder arthroplasty (TSA)?

RECOMMENDATION: Specific patient medical comorbidities and demographic factors are potential risk factors for shoulder PJI and appropriate preoperative evaluation and perioperative management should be standard practice.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

PJI after both primary and revision shoulder arthroplasty remains a challenging and costly problem. It is important to recognize medical comorbidities as well as demographic factors that may be risk factors for shoulder PJI. Medical comorbidities can negatively impact surgical outcomes and lead to an increased risk of complications; however, there is limited evidence specifically linking medical comorbidities and shoulder PJI. There are some helpful general measures of health, including American Society of Anesthesiologist (ASA) grading, Charlson Comorbidity Index (CCI) and Functional Comorbidity Index (FCI), among others. These indices can often be linked to surgical outcomes and PJI, including shoulder PJI [1].

A literature review was performed to identify all studies regarding medical comorbidities and demographic factors that may be risk factors for shoulder PJI. Search terms "shoulder replacement," "shoulder arthroplasty," "infection," "comorbidities" and "risk factors" were utilized for PubMed and Google Scholar searches through February 18, 2018. All abstracts were reviewed and full text article review was completed for screening of relevant articles. Ultimately, 13 studies were included for final analysis.

Medical comorbidities that have been shown to be potential risk factors for shoulder PJI include American Society of Anesthesiologists (ASA) grade III or higher [1], rheumatoid arthritis [2], long term corticosteroid use [2], current and former smokers [3], Hepatitis C virus [4], HIV-positive [5], weight loss/nutritional deficiency [6], drug abuse [6] and iron deficiency [7].

Increased body mass index greater than or equal to 35 kg/m^2 has been associated with increased superficial wound infection but was not shown to be associated with shoulder PJI [8]. Patient demographic factors that have been shown to be risk factors for shoulder PJI include younger age [6,7,9–11] and male gender [6,8–11].

There is a limited but growing body of literature to support medical comorbidities and demographic factors that are potential risk factors for shoulder PJI. It is important to recognize and treat potentially modifiable medical comorbidities as well as counsel patients regarding additional non-modifiable comorbidities and demographic factors.

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Authors: Mark Frankle, Jason Hsu

QUESTION 2: Does previous shoulder surgery (arthroscopic or open non-arthroplasty) increase the risk of periprosthetic joint infection (PJI)?

RECOMMENDATION: Previous ipsilateral non-arthroplasty shoulder surgery likely increases the risk of shoulder PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Due to the inability of skin preparation solutions [1–3] and antibiotics [3–5] to eradicate bacteria (e.g., *Cutiibacterium acnes*) living underneath the skin surface, transection of the dermal structures leads to inoculation of bacteria into the deep tissues [6]. Therefore, previous non-arthroplasty surgery theoretically may increase the risk of PJI.

To answer this question, we performed a systematic review using the following search phrase: ("previous" OR "history of") AND "shoulder arthroplasty" AND ("infection" OR "culture"). Thirty-nine results were filtered by title and abstract, and reference lists were reviewed for relevant studies. Studies were included for analysis if they compared infection rates for shoulder arthroplasty in a group of patients with and without history of previous non-arthroplasty surgery. Studies that included previous arthroplasty (rather than non-arthroplasty) surgery as a risk factor were excluded.

Two studies have addressed the question of whether previous non-arthroplasty surgery increased the risk for shoulder PJI. Werthel et al. [7] looked at non-arthroplasty surgery as a risk factor for PJI and found that previous non-arthroplasty surgery was a risk factor for deep infection after both a univariate ($p = 0.0094$) and a multivariate analysis ($p = 0.0390$). An increased number of previous surgeries was associated with a greater risk of deep infection ($p = 0.272$).

Florschütz et al. [8] also reported that patients undergoing primary total shoulder with history of previous non-arthroplasty surgery had a significantly higher (p = 0.016) rates of infection compared to patients with no previous surgery on the operative shoulder.

A few other studies not aimed directly at answering this question directly support this conclusion. Foruria et al. [9] studied 107 patients with unexpected positive cultures at revision shoulder arthroplasty and found that the number of previous surgeries was higher in patients deemed to have "true infections" compared to "contaminants" (p = 0.025) (it is unclear if these were arthroplasty or non-arthroplasty surgeries). Horneff et al. [10] found that patients undergoing revision arthroscopic surgery had a significantly higher rate of positive culture growth than those undergoing primary arthroscopic surgery (29.4% vs. 3.2%). Zavala et al. [11] reported on their experience with deep infection after reverse shoulder arthroplasty and found an overall infection rate of 6% and an infection rate of 12.9% for those who had previous failed cuff surgery.

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Authors: Mark Frankle, Jason Hsu

QUESTION 3: Does prior corticosteroid injection increase the risk of periprosthetic joint infection (PJI) after primary or revision shoulder arthroplasty?

RECOMMENDATION: An increased number of corticosteroid injections and a shorter interval between corticosteroid injection and shoulder arthroplasty may increase the risk for surgical site infection or shoulder PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

It is well-documented that usual skin preparation solutions do not adequately penetrate below the skin surface to eliminate bacteria, such as *Cutibacterium* [1,2]. Therefore, any instrument transecting the skin surface and sebaceous glands can theoretically inoculate the deep tissues [3].

To answer the question of whether corticosteroid injections increase the risk for surgical site infection/PJI, we performed a systematic review using the following search phrase: ("corticosteroid" OR "steroid" OR "cortisone") AND "shoulder" AND ("arthroplasty" OR "replacement"). Fifty-two results were filtered by title and abstract, and reference lists were reviewed for relevant studies. Studies were included for analysis if they were a study on primary or revision shoulder arthroplasty and studied preoperative injections as a risk factor.

A total of four studies have directly investigated the effect of previous steroid injection on the shoulder – one database study, one clinical study and two studies investigating deep cultures.

Werner et al. [4] performed a Medicare database study that compared three groups: arthroplasty within three months after injection, arthroplasty within three and 12 months after injection and a control group. Infection was defined by ICD-9 and CPT codes for both superficial and deep infection. The odds ratio for infection after arthroplasty was 2.0 at both three months (p = 0.007) and six months (p = 0.001) in patients who underwent injection within three months of arthroplasty and controls. No statistical difference was seen comparing those patients who underwent injection 3-12 months prior to arthroplasty and the control group. This study suggests that patients undergoing arthroplasty within three months after injection have a higher risk of infection.

Rashid et al. [5] performed a retrospective matched cohort study of 23 patients undergoing shoulder arthroplasty with history of preoperative intra-articular corticosteroid injection and 60 patients without a history of injection. None of the patients in either group had a superficial surgical site infection, and only one of the patients had a deep surgical site infection (defined as obvious purulence).

Two other studies have investigated the rate of positive deep cultures at the time of primary open shoulder surgery in patients that have and patients that have not had previous corticosteroid injections. Mook et al. [6] prospectively collected data on 104 patients undergoing open shoulder surgery at which time control

and pericapsular tissue samples were cultured. A history of two or more corticosteroid injections had a higher likelihood of bacterial growth than those with one or less injections ($p = 0.047$). Koh et al. [7] retrospectively analyzed 30 patients undergoing primary shoulder arthroplasty at which time superficial and deep wound swabs were taken. Steroid injection was not statistically significantly associated with positive deep cultures ($p = 0.14$), and the presence of hair in conjunction with previous steroid injection was not statistically significant ($p = 0.092$).

While the evidence in the hip arthroplasty literature is somewhat conflicting [8–10], multiple recent studies from the knee arthroplasty literature support the conclusion that corticosteroid injections before arthroplasty increase the risk for PJI [11,12].

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1.4. PREVENTION: SKIN PREPARATION

Authors: Ben Clark, Vani Sabesan, Arjun Meiyappan

QUESTION 1: Is there a role for preoperative skin scrub (home scrubs and washes) prior to primary or revision shoulder arthroplasty?

RECOMMENDATION: Chlorhexidine gluconate (CHG) showers or cleansing wipes with at least two applications decreases the incidence of positive skin cultures prior to shoulder surgery. Pending further research, this protocol may provide a benefit.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A systematic review of the published literature was performed on Scopus, PubMed and Cochrane databases that included any primary or secondary aims regarding preoperative skin prep for shoulder arthroplasty. A comprehensive review and list were accumulated and review was done to include all relevant studies that met these specific criteria.

Surgical site infections (SSIs) account for 14-16% of all nosocomial infections [1]. In an effort to reduce SSI's, protocols have incorporated whole body showering or bathing with CHG and other antiseptics. The aim is to cleanse the skin and reduce the cutaneous bacterial load prior to surgery. Previous studies have found reduced bacterial counts after use of chlorhexidine baths or washes with increased effect after multiple applications [2].

However, there has been much debate on this issue with various organizations expressing different views on the matter. The Centers for Disease Control and Prevention (CDC) has indicated that either soap or other antiseptic agents are equally efficacious as CHG. While the hospital infection control practice advisory committee – CDC recommend that patients shower at least one time with any kind antiseptic. Finally, the Institute for Healthcare Improvements – Project JOINTS recommends that patients should bathe or shower with CHG soap for at least three days prior to surgery [3].

Multiple interventional studies have investigated the use of preadmission CHG showers. Eiselt et al. focused on preoperative CHG cloths twice prior to total joint procedures and found that surgical site infections were significantly reduced from 3.19% to 2% when compared to a no wash group this was a significant reduction of 50.2% in SSIs [4]. Johnson et al. studied the use of at home chlorhexidine impregnated skin preparation cloth in decreasing the incidence of deep periprosthetic hip arthroplasty. Of the 1,134 studied, 157 complied with the preoperative chlorhexidine preparation protocol. There was no significant difference in the infection rates between the non-compliant and compliant groups (1.6% infection rate vs. 0% respectively; $p = 0.231$) [5]. Kapadia et al. evalu-

ated 557 patients who used preoperative chlorhexidine cloths and 1901 patients who did not. There was a statistically significant lower infection rate among the patients who used the cloths (0.5%) when compared to patients who did not (1.7%) [6].

Murray et al. explored the use of 2% chlorhexidine no rinse clothes used twice before any type of shoulder surgery in a prospective randomized trial of 100 patients with a control group that used only soap. Cutaneous cultures were taken before surgery and patients were monitored for postoperative infections. There were no infections in either group. The positive culture rate was 66% in the treatment group and 94% (p = .0008) in the control group, and the positive culture rate for coagulase-negative *Staphylococcus* was 30% and 70% respectively (p = .0001) [7].

In general, most studies have focused on hip and knee replacement surgery rather than shoulder surgery. However, the studies referenced above demonstrate the efficacy of CHG-containing products when applied at a minimum of two applications. Despite weak recommendations by the CDC, clinical evidence supports a minimum of two preadmission 4% CHG showers or no-rinse 2% CHG cloth applications as a critical component of a broader interventional strategy for reducing the risk of SSIs in shoulder surgery [3,8].

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QUESTION 2: What is the optimal perioperative surgical skin prep for primary or revision shoulder arthroplasty?

RECOMMENDATION: The best available evidence supports 2% chlorhexidine gluconate and 70% isopropyl alcohol for surgical skin prep for shoulder arthroplasty.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive search of several databases from 1988 to January 15th, 2018 (any language) was conducted. The databases included Ovid Medline Epub Ahead of Print, Ovid Medline In-Process & Other Non-Indexed Citations, Ovid Medline, Ovid Embase, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for surgical site preparation for prosthetic shoulder joint infections. The complete search strategies are listed below.

The rationale for the use of chlorhexidine surgical prep prior to shoulder arthroplasty is based on one level-I randomized controlled trial by Saltzman et al. [1]. In this trial, patients were randomized to compare ChloraPrep™ (Becton Dickinson) (2% w/v chlorhexidine gluconate (CHG) in 70% v/v isopropyl alcohol (IPA)), DuraPrep™ (3M™) (Iodine Povacrylex (0.7% available iodine) and isopropyl alcohol, 74%), and povidone-iodine ((0.75% iodine scrub and 1.0% iodine paint; Tyco Healthcare Group, Mansfield, Massachusetts) for patients undergoing shoulder surgery. The rate of positive skin cultures was reduced but not eliminated with ChloraPrep™ (7%) when compared with DuraPrep™ (18%) or povidone-iodine (31%). Furthermore, there were no infections in any of the patients at a mean of 10 months follow-up. In this trial, while a chlorhexidine solution was most active against the bacteria on the shoulder in general, there was no significant difference detected among the agents in their ability to eliminate *Cutibacterium acnes* from the shoulder region [1]. As *Cutibacterium acnes* is increasingly recognized as a key player in shoulder periprosthetic joint infection (PJI), there is concern that the current prep solutions are inadequate to treat this pathogen. Despite this, there were no postoperative infections in any of the groups at a minimum of 10 months of follow-up.

Chlorhexidine waterless wipes have also been advocated to decrease bacterial burden preoperatively. Murray et al. in another level-I study randomly assigned patients to one of two groups. Group 1 wiped the shoulder with 2% chlorhexidine gluconate impregnated cloths and group 2 showered with soap and water before surgery [2]. Again, none of the patients developed a postoperative infection and the cultured sites on the skin showed a reduction in positive cultures for coagulase-negative *Staphylococcus* and *Cutibacterium acnes*. Nevertheless, others have found the persistence of *Cutibacterium* within the skin dermis despite standard skin prep with chlorhexidine [3–7]. There is significant literature establishing a high rate of *Cutibacterium acnes* positive surgical sites despite standard skin preparation in both the primary and revision settings, likely due to the fact that

TABLE 1. Search strategy

#	Searches	Results
1	Arthroplasty, Replacement/	6266
2	exp joint prosthesis/	96013
3	exp shoulder/	44325
4	exp Shoulder Joint/	50050
5	(1 or 2) and (3 or 4)	3220
6	exp shoulder arthroplasty/	2921
7	exp shoulder prosthesis/	997
8	exp Arthroplasty, Replacement, Shoulder/	1056
9	exp shoulder/su	3240
10	exp Shoulder Joint/su	7682
11	((“glenohumeral joint” or “glenoid labrum” or “humeroscapular joint” or “scapulo humeral joint” or “scapulohumeral joint” or shoulder) adj4 (prosthe* or implant* or reconstruc* or replacement* or arthroplast* or “artificial joint*” or surg* or operation* or reconstruct* or procedure*)).ti,ab,hw,kw.	21875
12	5 or 6 or 7 or 8 or 9 or 10 or 11	27190
13	exp Preoperative Care/	99126
14	exp SKIN/	487534
15	13 and 14	692
16	(((“Anti-infective*” or Antiinfective* or antiseptic* or “anti-septic*” or antimicrobial* or “anti-microbial*” or antisepsis or “anti-sepsis” or disinfect* or steriliz*) adj3 (agent* or prep* or product* or solution* or topical* or skin or cutaneous*)) or ((preop* or “pre-op*” or protocol*) adj5 (skin or cutaneous*)) or ((surgical or operative or skin or cutaneous* or steriliz* or disinfect*) adj3 prep*) or ((wound* or skin or cutaneous*) adj5 (contaminat* or infect* or steriliz* or disinfect*)) or (local* adj3 Infect*) or alcohol or “benzoyl peroxide” or Chlorhexidine or DuraPrep or “hydrogen peroxide” or iodophor* or iodopovidone or “microbial skin burden*” or “povidone-iodine” or “PVP-I” or “site prep*” or “Surgical drape*” or “Surgical-Site Infection*”).ti,ab,hw,kw.	1406854
17	15 or 16	1407106
18	12 and 17	581
19	(case adj3 report).mp,pt.	2235257
20	18 not 19	544
21	limit 20 to (letter or conference abstract or editorial or erratum or note or addresses or autobiography or bibliography or biography or blogs or comment or dictionary or directory or interactive tutorial or interview or lectures or legal cases or legislation or news or newspaper article or overall or patient education handout or periodical index or portraits or published erratum or video-audio media or webcasts) [Limit not valid in Embase,CCTR,CDSR,Ovid Medline(R),Ovid Medline(R) Daily Update,Ovid Medline (R) In-Process,Ovid Medline (R) Publisher; records were retained]	38
22	from 21 keep 36	1
23	(20 not 21) or 22	507
24	limit 23 to yr=“1980 -Current”	496
25	remove duplicates from 24	348

the preparation solutions do not adequately penetrate the deep dermal sebaceous glands where *C. acnes* resides [5,8].

Benzoyl peroxide (BPO), which has known bactericidal properties against *C. acnes,* has been investigated for use in shoulder surgery [9–11]. BPO is a lipophilic compound directly toxic to both surface and ductal bacteria via penetration of pilosebaceous ducts. Once applied to the skin, the decomposition of BPO creates free oxygen radicals, which have potent bactericidal activity directly within the sebaceous follicles. In a study by Sabetta et al., patients were randomly assigned to wipe the surgical site with 5% topical benzoyl peroxide 48 hours before arthroscopic surgery [10]. These authors found five applications of BPO were effective in reducing *C. acnes* on the skin at the beginning and end of surgical procedures. A more recent randomized controlled single-blinded trial by Scheer et al. was performed utilizing BPO applications versus chlorhexidine wipes and subsequent chlorhexidine surgical scrub on the ability to reduce bacteria cultured from skin over a deltopectoral approach in healthy volunteers [11]. BPO applications were also performed 48 hours prior to culture in this study and samples taken before and after standard surgical prep with chlorhexidine. These authors found cultures remained negative for up to two hours after application in the BPO group. As these were healthy volunteers without a surgical intervention, no clinical effect could be measured.

A topical preparation of BPO combined with clindamycin applied in the evenings prior to surgery may be an alternative method to decrease bacterial load, particularly of *Cutibacterium acnes*, in the setting of shoulder surgery. In a level II prospective cohort study of patients undergoing shoulder arthroscopy, Dizay et al. found a statistically significant decrease in *Cutibacterium acnes* colonization of the skin at the time of surgery, particularly when more than one application was used leading up to surgery [9].

Despite the positive findings of the above studies of BPO in reducing *C. acnes* on the skin, none have shown a clinical reduction in infections in arthroplasty patients. Therefore, a clinical trial in this specific patient population is needed.

In order to be effective, skin preparations must cover the skin of the surgical site. One level III investigation by Syed et al. examined the type of application of the prep and found that simple gauze pads were more effective at completely covering the skin than the prep sticks alone [12]. In this study, 22 shoulders of volunteer subjects were prepped with either an applicator stick or two sterile 4x4 cm gauze sponges. ultraviolet-A light and advanced image-analysis software were utilized to determine areas of the skin that remained un-prepped. The applicator stick method resulted in a statistically higher percentage of un-prepped skin than the gauze sponge method and the axilla was the most likely to have un-prepped areas. Nevertheless, this study did not explore the infection implication in the difference between the applicator stick and the gauze sponges, and thus a clinical study is needed prior to making any definitive recommendations.

Other ancillary methods surrounding the skin prep such as axillary hair clipping have not been shown to decrease the bacterial burden or clinical infection rate. In fact, Marecek et al. found that there was a significantly greater bacterial burden in the clipped shoulder compared with the unclipped shoulder before preparation, but this effect was not found after surgical preparation. Importantly, all shoulders showed a significant reduction in total bacterial load, including *Cutibacterium acnes,* for both axillae after surgical preparation with 2% CHG and 70% IPA [13].

There is limited evidence specifically dealing with revision shoulder arthroplasty and skin prep. In an attempt to "seal off" pores and isolate remaining bacteria on and in the skin from the wound during revision arthroplasty, Lorenzetti et al. in a level III study examined the use of cyanoacrylate prior to barrier drapes. The skin edges were painted with the glue over the area of the planned incision and allowed to dry prior to the placement of barrier drapes. This study showed that the prevalence of cases with positive intraoperative cultures decreased from 18% in the standard prep and iodoform barrier drape to 7% in the group with a cyanoacrylate barrier, but this difference did not reach statistical significance [8]. While noteworthy, this was a single level III study and authors were careful to point out that it was underpowered to make generalizable conclusions. Thus this technique, while the only one specifically addressing skin prep techniques during revision shoulder arthroplasty, requires further study before recommending its use.

Web of Science

1. TOPIC: (((“glenohumeral joint” or “glenoid labrum” or “humeroscapular joint” or “scapulo humeral joint” or “scapulohumeral joint” or shoulder) NEAR/4 (prosthe* or implant* or reconstruc* or replacement* or arthroplast* or “artificial joint*” or surg* or operation* or reconstruct* or procedure*))) AND TOPIC: (((((“Anti-infective*” or Antiinfective* or antiseptic* or “anti-septic*” or antimicrobial* or “anti-microbial*” or antisepsis or “anti-sepsis” or disinfect* or steriliz*) NEAR/3 (agent* or prep* or product* or solution* or topical* or skin or cutaneous*)) or ((preop* or “pre-op*” or protocol*) NEAR/5 (skin or cutaneous*)) or ((surgical or operative or skin or cutaneous* or steriliz* or disinfect*) NEAR/3 prep*) or ((wound* or skin or cutaneous*) NEAR/5 (contaminat* or infect* or steriliz* or disinfect*)) or (local* NEAR/3 Infect*) or alcohol or “benzoyl peroxide” or Chlorhexidine or DuraPrep or “hydrogen peroxide” or iodophor* or iodopovidone or “microbial skin burden*” or “povidone-iodine” or “PVP-I” or “site prep*” or “Surgical drape*” or “Surgical-Site Infection*”)) AND DOCUMENT TYPES: (Article OR Abstract of Published Item OR Proceedings Paper OR Review) Indexes=SCI-EXPANDED, ESCI Timespan=1980-2018
2. TS=(case NEAR/3 report)
3. 1 NOT 2
4. PMID=(0* or 1* or 2* or 3* or 4* or 5* or 6* or 7* or 8* or 9*)
5. 3 NOT 4

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QUESTION 3: Is there a role for topical skin treatments prior to primary or revision shoulder arthroplasty?

RECOMMENDATION: At this time, there is no evidence for or against the use of topical skin treatments to reduce the rate of shoulder periprosthetic joint infection (PJI).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The use of chlorhexidine gluconate (CHG) topical skin treatment preoperatively has been recommended by the International Consensus on Periprosthetic Joint Infection. However, specific to shoulder arthroplasty, the use of topical skin treatments has not been shown to significantly reduce the superficial bacterial load of *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*), nor reduce culture positivity of deep samples retrieved from the surgical site during primary shoulder arthroplasty [1–6].

C. acnes has been reported as the most common pathogen in shoulder PJI and, as well as being present on the skin, is also present within the sebum-rich pilosebaceous hair follicles of the deep dermis, making it difficult to eradicate with topical antiseptic techniques. Surgical incisions, transecting thousands of these *C. acnes*-filled dermal glands, can lead to contamination of deeper tissues.

C. acnes is also implicated in the pathogenesis of acne vulgaris for which the anti-bacterial agent benzoyl peroxide (BPO) has been used as topical therapy. BPO releases free-radical oxygen which oxidizes bacterial proteins in the sebaceous follicles, decreasing the burden of anaerobic bacteria in the deeper tissues and also inflammation due to the reduction of irritating-type free fatty acids. Leyden described a 90% reduction in *P. acnes* after 48 hours of topical treatment and a 99% reduction after 72 hours of treatment [7]. The addition of topical clindamycin phosphate 1.2% has also been demonstrated to further decrease bacterial load [8]. Although BPO with clindamycin may therefore be the optimal treatment for use prior to shoulder surgery to decrease *C. acnes* contamination, further research is needed to correlate superficial decontamination with decreased infection rates and shoulder PJI [9].

Specific to primary shoulder joint replacement, Levy et al. reported 23 of 55 patients had *P. acnes* growth in the joint synovial fluid collected during surgery [10]. Despite their protocol of washing the shoulder, arm and axilla with 4% CHG, they reported high incidence of *P. acnes* [10]. Other recent studies evaluated colonization rates for primary shoulder arthroplasties and found around 70% of cases had positive cultures for *C. acnes* despite using CHG, and patients of male gender and those with body hair had higher rates of superficial *C. acnes* [4,5,11,12]. In study by Koh et al., 30 patients undergoing primary shoulder arthroplasty had superficial swabs and deep tissue samples sent for culture at various stages of the operation following CHG application. After the chlorhexidine skin scrub in the operating room, 40% (12/30) had positive skin swab cultures and 27% (8/22) after dual application of chlorhexidine to the skin. Forty-three percent had positive deep cultures on entering the glenohumeral joint, and deep cultures after implantation of the prosthesis were positive in 37%. After closure, 43% had positive superficial cultures. In total, 73% of patients had positive cultures and the authors concluded that topical antiseptic measures did not completely eliminate *C. acnes* [12]. Despite its proven antiseptic effects, dermal application of aqueous CHG during shoulder surgery fails to eradicate or reduce *C. acnes* on deep cultures. The current literature is limited by the lack of high quality studies which can provide definitive answers regarding the clinical effectiveness of various CHG preparations preventing prosthetic shoulder joint infections [13].

Sabetta et al. described the preoperative application of topical 5% BPO in addition to the standard use of CHG preoperative skin preparation to reduce *C. acnes* rates in patients undergoing arthroscopic shoulder procedures. BPO was applied twice daily for a total of 5 applications in the 48 hours prior to operation in 50 patients undergoing primary arthroscopic shoulder surgery [14]. Sixteen percent (8 of 50) of skin swab cultures surgical skin prior to preparation with ChloraPrep from the anterior deltoid of the BPO-treated arm were positive, compared with 32% (16 of 50) of the skin on the anterior deltoid of the untreated arm ($p = .001$). The addition of BPO cream to their standard ChloraPrep protocol appeared to provide an improved method of skin cleansing; however, due to the design of the study (non-randomized), differences in deep culture rates could not be determined [14]. Dizay et al. prospectively studied 65 patients undergoing shoulder arthroscopy using topical 5% benzoyl peroxide plus clindamycin phosphate 1.2% (BPO/C) [15]. The preparation was applied for more than two days prior to surgery. Skin surface swab cultures were taken preoperatively and in the operating room before the standard chlorhexadine preparation. A third set of cultures were taken by swabbing the shoulder tissue at the operative site under direct arthroscopic visualization through an arthroscopic cannula upon completion of the procedure. The topical gel was effective in eliminating 74.2% (23 of 31 patients with positive preoperative

cultures) of *C. acnes* skin colonization by day of surgery. The rate of positive cultures from the deep shoulder joint was 3.1% (2/65 patients) with preoperative BPO/C topical treatment, much lower than similar studies which described up to 19.6% positive deep cultures [9,15].

In summary, there is evidence that topical skin treatments can reduce bacterial loads, such as *C. acnes*. However, no studies examined the effect of skin preparations on the most clinically significant end-point—the rate of shoulder PJI. The use of topical BPO with or without clindamycin, whilst encouraging and warranting further study, cannot currently be fully endorsed as standard practice for prevention of shoulder PJI, until further data is available.

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QUESTION 4: Should the subcutaneous and dermal tissues be disinfected during shoulder arthroplasty?

RECOMMENDATION: There is insufficient evidence for or against disinfection of the subcutaneous and dermal tissues during shoulder arthroplasty.

LEVEL OF EVIDENCE: No Evidence

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A review of PubMed "(subcutaneous OR irrigation OR disinfection OR topical OR local) AND shoulder AND arthroplasty)" and Google Scholar "shoulder arthroplasty subcutaneous irrigation disinfection topical local" was performed to identify articles comparing strategies for disinfection of the subcutaneous and dermal tissues during shoulder arthroplasty. No such literature was identified. In the absence of specific evidence, basic science research and research in other fields of surgery were reviewed.

Lee et al. [1] performed punch biopsy cultures from the shoulders of volunteers after standard surgical preparation of the skin. Seven of ten subjects revealed positive cultures for *Cutibacterium*. On this basis, the authors concluded that surgical preparation could leave bacteria under the surface of the skin, and further disinfection should be performed.

In a retrospective hip and knee arthroplasty series, Brown et al. [2] compared dilute betadine lavage prior to closure of total hip and knee arthroplasty incisions to controls. The deep infection rate was lower in the group undergoing betadine lavage compared to the control group. In contrast, a similar methodology using chlorhexidine gluconate (CHG) showed no difference between CHG irrigation groups and controls. However, the conclusions may have been confounded by the fact that povidone-iodine was also utilized in the control group [3]. A broader meta-analysis of randomized controlled trials across various surgical specialties found that lavage with dilute betadine reduced the occurrence of surgical site infections in the majority of trials with no reported complications [4].

An intra-articular injection of gentamicin [5] and the application of topical vancomycin powder [6] have also both been described as operative measures to reduce periprosthetic joint infection in shoulder arthroplasty. Although there was no clinical evidence for the use of vancomycin powder in the shoulder, recent literature in the field of spinal surgery has shown a significantly decreased risk of surgical site infection with the use of topical vancomycin

[7]. A retrospective review of 507 shoulder arthroplasty procedures compared 343 patients who received an intra-articular injection of 160 mg gentamycin at the end of surgery to 164 patients who did not; the infection rate in the control cohort was 3% (5 of 164) compared to 0.3% (1 of 343) in the gentamycin cohort [5]. However, the design of the study allowed for bias with confounding variables, including the use of antibiotic impregnated cement, which may have influenced outcomes.

It should be noted that the Centers for Disease Control and Prevention released a recommendation on the use of vancomycin in 1995. Due to concerns for development of antimicrobial resistance, routine utilization of vancomycin in prophylaxis has been discouraged. Instead, use of vancomycin is believed to be acceptable for "prophylaxis for major surgical procedures involving implantation of prosthetic materials or devices at institutions that have a high rate of infections caused by MRSA or methicillin-resistant S. epidermidis." This position statement has not been updated recently or amended to include a discussion of vancomycin powder.

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Diagnosis

2.1. DIAGNOSIS: CULTURE SIGNIFICANCE

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QUESTION 1: What is the relevance of positive cultures in the evaluation for shoulder periprosthetic joint infection (PJI)? What defines a clinically relevant positive culture result(s) versus a culture contaminant?

RECOMMENDATION: Positive cultures in a patient with painful or failed shoulder prosthesis should be considered and treated appropriately based upon the clinical context and diagnostic criteria.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A bacterial infection is most rigorously defined as "bacteria doing harm." This definition is not met by either (a) harm without the documentation of bacteria (e.g., a culture-negative draining sinus from fat necrosis or implant material allergy) or (b) bacteria in the absence of harm (e.g., *Cutibacterium* in the sebaceous glands of the normal dermis) [1,2].

Five factors need to be considered when evaluating the results of tissue and explant cultures in a case of suspected periprosthetic shoulder infection.

1. The importance of the denominator [3]; the chances of obtaining positive cultures rises with the number of specimens submitted for culture. For example, if the indication for treatment is two or more positive cultures and if one of three submitted specimens is culture positive, the criterion is not met. If, however, six specimens from the same shoulder are submitted, it is likely that two would be positive and the criterion would be met.
2. The source of the specimen affects the likelihood of a positive culture: explant and tissue specimens are more likely to be culture positive than joint fluid specimens from the same shoulder [4,5].
3. The media used in culturing of a specimen affect the likelihood of the specimen being culture positive. The use of multiple media, including broth and aerobic and anaerobic agar preparations is most likely to reveal the presence of bacteria [5].
4. Cultures are not simply "positive" or "negative." While some positive cultures grow out only one colony on a plate or are only positive in the broth, others have 2+ or more growth on agar plates, indicating a much greater bacterial load [6].

   Shoulders with higher bacterial loads are likely to have a higher percentage of specimens that are culture positive. Specimens with a high bacterial load are likely to have a shorter time to the point when the laboratory reports a positive culture result [7].
5. Cultures reveal the presence of live bacteria. It is important to consider the possibility that the specimen might have been contaminated from the operating room environment by inadvertent contact with the skin, unsterile instruments or accidental exposure in handling in the microbiology laboratory. Several precautions can be helpful in minimizing the risk of specimen contamination, including using new sterile instruments for each specimen, avoiding skin contact with the specimen and culturing sterile specimens (e.g., sponges or swabs opened in the operating room (OR)) to assess the rate of positive control cultures.

Mook et al. [8] reported a 13% positive control culture rate using a sterile sponge exposed to the air in the OR. Sabetta et al. reported a 4% culture positive rate for a cotton swab exposed to air as a control [9]. MacNiven et al. [10] found that 50 control swabs exposed to the air were all negative using a threshold Specimen Propionibacterium (*Cutibacterium*) Value (SPV) of ≥ 1. Because the rate of positivity of control samples obviously varies from center to center, it would seem essential that each shoulder service should periodically submit sterile specimens to determine its rate of positive control cultures.

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QUESTION 2: What is the relevance of unexpected positive cultures (UPC) in revision shoulder arthroplasty without clinical or radiographic signs of infection?

RECOMMENDATION: The relevance of unexpected positive cultures is unknown.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive literature review was performed to identify all studies on UPC in shoulders undergoing revision arthroplasty. Searches for the terms "unexpected," "infection," "positive culture," "indolent infection," "gram-positive bacterial infections," "prosthesis-related infections" and "shoulder joint," "shoulder," "arthroplasty," "total joint," "replacement," "periprosthetic," "peri-implant," "shoulder prosthesis" were performed using the search engines PubMed, Embase and Scopus. These searches were conducted on February 2, 2018 and include results published through that time. Inclusion criteria were patients undergoing revision shoulder arthroplasty, with no clinical or radiographic signs of infection, who had positive cultures taken from the shoulder undergoing the revision. Only studies that focused on the potential relevance of these UPCs were included. Only English-language studies that presented original data on more than five patients meeting inclusion criteria were included. For articles with both unexpected positive cultures and known septic revisions, the patients with UPC were included in the review if the data were reported such that patients meeting inclusion could be separated. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed. Fifteen articles met inclusion and exclusion criteria.

At the time of the writing of this document, the definition of a UPC in shoulder arthroplasty revisions has not been fully elucidated, nor has the role of *Cutibacterium acnes*, a commonly identified microorganism. Few studies have been designed to adequately capture this phenomenon as defined above by the inclusion and exclusion criteria, resulting in a challenge to draw any definitive conclusions. The results of studies that report the frequency of UPC and their characteristics are summarized in Table 1 [1–14]. An additional study [15] was also returned that does not provide data appropriate for Table 1, but nonetheless was relevant to this question and is discussed below.

Few studies fully meet the defined inclusion and exclusion criteria, and little consistency exists on the definitions of "unexpected" or even what constitutes a "true positive" culture. Without agreement on this definition, it is exceedingly challenging to compare studies reporting these rates. In some studies, "true positive" was defined as a shoulder that required re-revision whereas in other studies, evidence of an overt infection postoperatively was used. While both outcomes are clinically significant, the association of positive cultures with them cannot be conclusively characterized as causal.

The studies that identified UPC in shoulder arthroplasty revisions report a range from 9–56% of cases [5,6]. Combining the rates of UPCs in these studies yields an incidence of 22.5% (305 UPC out of 1,354 shoulder arthroplasty revisions). *C. acnes* was identified in 53.8% (164 of 305) [2,3,5,7,8,13,14]. The results presented by Pottinger et al. [6] were not included in these sums as the same data was included in Lucas et al. [13].

Other reports that did not evaluate UPCs in the setting of shoulder arthroplasty revision but did address the relevance and the baseline rate of positive *C. acnes* cultures in shoulders were included in our search results. Mook et al. found that 20.5% of shoulders undergoing open surgery for a variety of conditions had at least one positive culture (83.0% of which were *C. acnes*), but this rate was not significantly different from UPC rates from their control, "sterile" gauze cultures (13.0%) [16]. At this particular institution, the "false positive rate"—defined as the rate of positive cultures for "sterile" gauze sponges—was 20.5%, with the majority positive for *C. acnes*. These numbers should be compared with the overall rate of UPC in revision shoulder arthroplasty found in this review (22.5%) and with 53.8% positive for *C. acnes*. The detection of *C. acnes* on surgical equipment was replicated by Falconer et al. who, immediately after skin incision in shoulder without prior surgery, swabbed the subdermal layer, the surgeon's glove tip, the scalpel blades and the forceps to determine possible vectors for introduction of this bacteria to the deep shoulder. Where cultures are taken, *C. acnes* was detected on at least one of these cultures in 40% of their patients, with the subdermal layer being the most common origin of positive cultures, followed by the surgeon's glove and forceps. The fact that the within-subject positive culture rate of both of these sites was significantly correlated with positive subdermal cultures led the authors to suggest that it is the surgeon's manipulation of skin during a procedure that ultimately causes contamination of the deep shoulder with this organism [17]. Levy et al. similarly found *C. acnes* in 41.8% of shoulders undergoing primary shoulder arthroplasty for osteoarthritis following standard

chlorhexidine preparation and draping. Interestingly, in contrast to Falconer et al., Levy et al. concluded that this bacterium may not be a contaminant, but instead perhaps plays a role in the pathogenesis of glenohumeral arthritis [18].

To further determine if these positive results represent true positive or false positive results, we evaluated the rate of "true" infections using each author's own criteria. However, these definitions were not consistent across studies, presenting an obstacle that requires the clinician to use his or her judgment as to the most appropriate definition of true infection until a standard definition can be established. In some studies, repeat culture taken at either re-revision or as part of follow-up that demonstrates presence of the same organism was required to define a UPC as a true infection [7–9]. In other studies, signs or symptoms of infection post-revision were sufficient [5,14]. With this methodological caveat regarding the lack of a consistent definition for infection in mind, five studies [3,5,7,8,14] reported a "true" infection rate. When combined, only 18 of 168 total UPCs (10.7%) were considered "true," and, of those 18, 14 (77.8%) were *C. acnes*.

To determine the likelihood that UPCs represent a contaminant, McGoldrick et al. examined 148 cases to identify 14 shoulders with a UPC on revision that occurred at least 3 years following the initial arthroplasty with a mean time to revision of 8 years (range 4–12). They found that 79% of the 109 cultures they obtained grew *Cutibacterium* and concluded that a percentage this high implies that these cultures represent true infections of the shoulder and not contamination. McGoldrick et al. also pointed out that these positive cultures should truly be considered "unexpected" as many of the patients had factors well known to be correlated with positive *C. acnes* cultures, such as male gender, pain and stiffness [10].

Frangiamore et al. evaluated the time to positive culture in an attempt to differentiate "probable true positives" from "probable contaminants." Using their definitions, they found that the cultures of "probable true positives" grew bacteria by 11 days. Conversely, 44% of cultures of "probable contaminant" cases became positive after 11 days. The median time to growth among "probable true positives" was five days, compared to the nine days for the "probable contaminants." Their conclusion points out a potential downside to the increased sensitivity of long-hold cultures for *C. acnes* – this may also come with an increased risk of contamination and false positives. However, again, without a clear definition or a confirmatory test, it is not clear if the late growth cultures were really contaminants or simply had a lower inoculum of bacteria [9].

Pottinger et al. [6] evaluated potential risk factors for UPC in shoulder arthroplasty revisions across three phases of management: preoperative findings, gross intraoperative inspection upon entering the shoulder and histological examination. On multivariate analysis, they found that male sex (odds ratio (OR) 6.41, 95% confidence interval (CI) 3.10 – 14.42), and humeral osteolysis on X-ray (OR 12.85, 95% CI 2.92 – 92.53) were significantly more likely to grow *C. acnes,* while individuals with diabetes (OR 2.80, 95% CI 1.20 – 6.64), a history of smoking (OR 2.88, 95% CI 1.27-6.62) and glenoid loosening on X-ray (OR 3.07, 95% CI 1.50 – 6.40) had increased odds of positive cultures with non-*C. acnes* bacteria. In addition, the presence of a membrane and cloudy fluid were associated with *C. acnes,* while glenoid loosening and chronic inflammatory signs on histology were predictive of UPCs with other bacteria. Increased numbers of cultures taken were associated with UPCs of both *C. acnes* and other bacteria [6].

Factors that were not significant predictors of either type of UPC included local and systemic symptoms, age, white blood cell count, erythrocyte sedimentation rate, C-reactive protein, acne, diabetes and a number of other medical conditions [6]. The number of prior surgeries was not found to be a predictor of UPC [6]. These findings contrast with the findings of Foruria et al. that patients with "true infections" had undergone significantly more previous operations than their "contaminant" cohort [8]. Further complicating the interpretation of UPCs is the difference across studies between the requisite number of cultures with growth for the shoulder to be included in analysis. While some authors require at least two UPCs [4,10,12], others, such as Grosso et al. [5] and Foruria et al. [8], included patients with as few as one positive culture. However, they found that the number of positive cultures was not associated with rate of "true" infection, as they define it. Their data does demonstrate, though, that, when positive cultures are unexpected, the majority of the shoulders only grow out in just one culture (76 of 107 patients), although this finding is clouded by the wide variation in the total number of samples taken per patient (93 of the 107 patients had 1–3 samples taken) [8].

While some authors have conjectured that scenarios where only a small number of cultures grow *C. acnes*, especially with a delayed incubation time [9], are more likely to represent a contaminant [4,16], other authors have noted that these may simply represent a lower quantity of bacteria present. Ahsan et al. introduced a semi-quantitative approach to assessing the bacterial load in an attempt to define a threshold to differentiate "true" infections from "contaminant." They recommended calculating a "Shoulder Propi Value" to represent the amount of growth per culture, combining these values into "Shoulder Propi Scores" for each specimen location, and then calculating the "Average Shoulder Propi Scores." They did not observe a threshold above which one could be confident that a culture was a true positive, and they highlighted the wide variation in culture results across specimen locations [15].

When considering the relevance of UPCs in the context of "true infections," there are two potential areas of clinical significance: the UPC may have been a subclinical pathogenic cause of the revision during which it was uncovered, or the UPC may go on to cause sequelae post-revision. Lucas et al. analyzed the former question in a study evaluating cultures taken from several sites within the shoulder. When considering UPCs from explanted glenoid components of the original arthroplasty, more of these components were loose at revision than were not. However, when considering all the cultures taken from a shoulder, there was no difference between the positive culture rates between the loose and not loose glenoid component groups [13]. In a study examining patients with glenoid component loosening but no evidence of infection otherwise, Cheung et al. evaluated the significance of UPCs both as potentially correlated with the need for the index revision where the UPC was identified and as potentially correlated with the need for future revision. They found that culture results were not associated with the need for the index revision, but they did note a trend towards a positive effect between UPCs and the need for further re-operation, though this did not reach significance ($p = 0.09$) [2].

There is no consistent definition that determines whether a positive culture represents a "true infection" or a "contaminant." One additional state exists; a positive culture could represent "commensal organisms"—present but not causing pain or pathology. Furthermore, while *C. acnes* represents the majority of positive UPC cultures, it is not clear if the relevance of a UPC with one bacterium differs from a UPC with another. The debate regarding the relevance of unexpected positive long-hold cultures will continue until a definition or confirmatory test allows clinicians and researchers to properly categorize these findings.

TABLE 1. Summary of studies examining unexpected positive cultures in shoulder arthroplasty revisions

Author, Year	Proportion of Shoulders with UPC at Revision	*C. acnes* among Patients with UPC	"True" Infections	Definition of "True" Infection	"True" Infection with *C. acnes*	Follow-up (revision/clinical failure) and Organism at that Time
Topolski 2006 [1]	75 UPC reviewed. Total population size is not described.	45/75 (60%)	10/75 (13%)	Required re-revision.	5/10 (50%)	10 total patients required re-revision for pain, instability, dislocation and infection.
Cheung 2008 [2]	20/68 (29%)	14/20 (70%)	Not described	Not described	Not described	Trend toward positive cultures predicting increased likelihood of surgery ($p = 0.09$) in group that did not have glenoid reimplantation. Organism at follow-up not described.
Kelly 2009 [3]	8/28 (29%)	6/8 (75%)	2/8 (25%)	Subsequent infection at minimum 1-year follow-up.	2/2 (100%)	Both infections treated with resection and placement of antibiotic cement spacer. Additional follow-up not described.
Dodson 2010 [4]	6 UPC in retrospective review of 11 patients with positive cultures. Total population size is not described.	6/6 (100%)	3/6 (50%)	Acute and chronic inflammation and granulation consistent with infection on pathology.	3/6 (50%)	All patients chose medical management, but long-term follow-up is not described.
Grosso 2012 [5]	17/187 (9%)	10/17 (59%)	1/17 (6%)	Recurrence with erythema and swelling.	0/1 (0%)	In only patient to develop post-revision infection, irrigation and debridement followed by > 5 weeks of antibiotic therapy successfully maintained aseptic shoulder for at least 5 years. Offending organism was the same as original positive culture, *Staphylococcus epidermidis*.
Pottinger 2012 [6]	108/193 (56%)	75/108 (69%)	Not described	Not described	Not described	Not described
Lorenzetti 2013 [7]	8/55 (15%)	6/8 (75%)	3/8 (38%)	Positive cultures and/or purulence at re-revision.	1/3 (33%)	Of three post-revision infections, all from the control group, *C. acnes* was confirmed in one and underwent re-revision.
Foruria 2013 [8]	107/678 (15%)	68/107 (64%)	11/107 (10%)	Positive culture with same organism as initial culture, taken post-revision, obtained via aspiration or during re-revision.	10/11 (91%)	8 of the 11 true infections underwent re-revision.

TABLE 1. Summary of studies examining unexpected positive cultures in shoulder arthroplasty revisions (*Cont.*)

Author, Year	Proportion of Shoulders with UPC at Revision	*C. acnes* among Patients with UPC	"True" Infections	Definition of "True" Infection	"True" Infection with *C. acnes*	Follow-up (revision/clinical failure) and Organism at that Time
Frangiamore 2015 [9]	26 UPC of 46 studied shoulders, all of which had positive cultures. Total population size is not described.	26/26 (100%)*	17/26 (65%) described as probable true positive	Probable true infection among UPC defined as > 1 positive culture.	17/17 (100%) *	Not described
McGoldrick 2015 [10]	14 UPC at revision at least 3 years after index arthroplasty. Total population size is not described.	14/14 (100%) **	Not described	Not described	Not described	Not described
Piggot 2015 [11]	8 UPC of 24 studied shoulders, all of which had positive cultures. Total population size is not described.	8/8 (100%)*	1/8 (13%)	For UPC, definite infection is defined as at least 2 positive cultures with no other organisms.	1/1 (100%)*	4/8 (50%) UPC had favorable clinical outcome; 3/8 (38%) did not have a favorable clinical outcome, and 1/8 (13%) was lost to follow-up.
Hsu 2016 [12]	27/55 (49%), where "positive" was defined as at least 2 positive Propionibacterium cultures.	27/27 (100%) **	Not described	Not described	Not described	No difference between revision rate, functional or pain scores between positive-culture and control cohorts. 3 from culture-positive cohort underwent re-revision and all cultures were negative at that time.
Lucas 2016 [13] ***	117/221 (53%)	45/117 (38%)	Not described	Not described	Not described	Not described
Padegimas 2017 [14]	28/117 (24%)	15/28 (57%)	1/28 (3.6%)	Recurrent infection	1/1 (100%) ****	No statistically significant difference in re-operation rates between UPC and non-UPC patients.

UPC, unexpected positive culture
* Only *C. acnes* cultures were studied.
** Only *Cutibacterium* were studied.
***This study is an addition of 137 cases to the cases already described in Pottinger et al. (6).
****Only 1/6 cultures for this patient grew *C. acnes*

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QUESTION 3: What is the treatment (if any) for unexpected positive cultures (UPC) in revision shoulder arthroplasty without clinical or radiographic signs of infection?

RECOMMENDATION: Unknown. Few publications offer protocols for addressing unexpected positive cultures. Of these, the most common options include antibiotics, re-operation and withholding any treatment. The lack of comparative data on outcomes of these therapy regimens makes it difficult to conclusively determine optimal management.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive literature review was performed to identify all studies on unexpected positive cultures (UPC) in shoulders undergoing revision arthroplasty. Searches for the terms "unexpected," "infection," "positive culture," "indolent infection," "gram-positive bacterial infections," "prosthesis-related infections" and "shoulder joint," "shoulder," "arthroplasty," "total joint," "replacement," "periprosthetic," "peri-implant," "shoulder prosthesis" were performed using the search engines PubMed, Embase and Scopus. These searches were conducted in February 2, 2018 and include results published through that time. Inclusion criteria included patients undergoing revision shoulder arthroplasty, with no clinical or radiographic signs of infection, who had positive cultures taken from the shoulder undergoing the revision. Only studies that focused on the potential treatment of these UPCs were included. Only English-language studies that presented original data on more than five patients meeting inclusion criteria were included. For articles with both unexpected positive cultures and known septic revisions, the patients with UPC were included in the review if the data was reported such that the patients meeting inclusion criteria could be separated. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed. Eight articles met inclusion and exclusion criteria.

Of the eight studies [1–8] returned that allude to treatment of UPCs, only six described their treatment protocol, but these do not allow for definitive conclusions to be drawn regarding the effect of each treatment type on outcomes, if any were reported (see Table 1) [1–6]. Despite neither providing a methodology for treatment assignment, nor results that were not in aggregate, Foruria et al. [3] noted that their duration of antibiotic treatment (range: 8-700 days) was not associated with the likelihood of a second positive culture during follow-up [3]. In the study by Hsu et al. [5], a more standardized treatment protocol was developed and applied to their sample of 55 patients. However, this study was limited by the use of a control cohort (that received a different treatment course) that may have had a single positive culture, thus making it challenging to answer the question of the best treatment for UPCs using these data. These investigators found that three patients in both the culture-positive cohort (defined as at least two UPC, n = 27) and the control cohort (zero or one UPC, n = 28) required a subsequent procedure. None of these three culture-positive cohort patients, who received the extended antibiotic regimen, had subsequent positive cultures at their revision, while one of three control cohort patients did [5]. Two studies do present this data, but it is not robust [7,8]. Few studies fully meet the defined inclusion and exclusion criteria, and many of these report results in an aggregate. Only two studies compare different treatment options using non-aggregated outcomes.

Padegimas et al. [7] compared individuals undergoing shoulder arthroplasty revision, 28 of which had UPC and 89 who did not. They noted that all patients received the authors' standard, postoperative empirical oral antibiotics for two weeks and then may continue to receive antibiotics for an additional six weeks depending on culture results, presentation and intraoperative findings. One of the 10 patients who did not receive the additional 6-week regimen had reinfection. Of note though, there were three other patients who did not have UPCs who developed reinfection as well. A higher percentage of UPC patients underwent reoperation (20.2%) than those without UPC (7.1%), but this difference did not reach statistical significance ($p = 0.109$) [7].

In the study by Piggot et al. [8], 8 shoulders of the 24 with positive *C. acnes* cultures that they studied were "unexpected" as defined by our inclusion criteria. The primary outcome used in this study was termed "a favorable clinical outcome," which was defined as a post-treatment improvement in pain and function and a lack of additional operations. This metric was assessed at the latest possible clinical visit. Four of these eight UPC patients met the favorable clinical outcome endpoint; three did not, and one was lost to follow-up. The antibiotics that each of these eight patients received varied by clinical judgment and susceptibility

TABLE 1. Summary of studies offering limited data on treatment and outcomes

Author	Number of Patients with UPC	Treatment Protocols	Outcomes
Kelly [1]	8	1 patient received 4 weeks of oral doxycycline for unrelated infection; 7 received nothing	2 late clinical infections, unclear if patient who received doxycycline was among them.
Dodson [2]	6	IV cefazolin for 36 hours postoperatively and clindamycin or penicillin upon culture result of *C. acnes* in all patients; oral ampicillin for 8-10 weeks in 5 patients; oral suppressive therapy for 24 months in 1 patient.	Patient on oral suppressive therapy had no signs of infection at time authors were writing. Outcomes not otherwise reported.
Foruria [3]	107	Variable; 34 patients were treated with antibiotic regimen (range 8-700 days) postoperatively; 19 were treated with chronic antibiotic suppression; 54 did not receive antibiotics other than preoperative prophylaxis.	Variable results mostly reported in aggregate; authors noted that duration of antibiotic regiment had no effect on likelihood of a repeat positive culture during follow-up.
Grosso [4]	17	13 patients received tobramycin or gentamicin impregnated cement; all received IV antibiotics for 24 hours postoperatively; no additional therapy following culture results.	1 clinical infection at 6 weeks postoperatively, confirmed as superficial wound infection during irrigation and debridement.
Hsu [5]	55 patients total; 27 were considered culture-positive with at least 2 positive cultures; 28 were considered the control cohort with 0 or 1 positive cultures	Variable; high-suspicion of infection patients received intravenous ceftriaxone for a minimum of 3 weeks; low-suspicion patients received oral amoxicillin and clavulanate for same minimum duration. If a patient became a culture-positive patient when more than 2 cultures became positive, the regimen was changed to intravenous ceftriaxone or vancomycin plus oral rifampin for 6 weeks followed by doxycycline or amoxicillin with clavulanate for a minimum of 6 weeks.	3 in the culture positive cohort required additional procedures, but none had positive cultures at re-revision; 3 in the control cohort also required subsequent procedures, and 1 of these 3 had a single positive culture. Further details about treatment duration on a patient-by-patient basis, beyond the general protocol already described, were not reported.
Topolski [6]	75	Variable; 54 patients received only the standard 2-3 doses of intravenous postoperative antibiotics and nothing further; 14 received additional, unspecified antibiotics (range 1-6 weeks); 7 received only oral, unspecified antibiotics.	10 required re-revision, 7 of which had positive cultures at that time, 5 of which were *C. acnes*. Further details about treatment duration on a patient-by-patient-basis were not reported.

UPC, unexpected positive culture

and is not well-reported. The addition of rifampin, and its duration, however, is well-documented. Of the four patients who had a favorable outcome, rifampin was added to the unspecified antibiotic regimen for each one with an average duration of 608.5 days (range 126–1,540 days). Of the three patients without a favorable clinical outcome, one received unspecified antibiotics plus rifampin for 196 days; one received unspecified antibiotics alone for 189 days, and one underwent surgery [8].

There is a clear need for additional research into treatment options for UPC. The comparative studies are weak and underpowered and a dearth of randomized controlled trials of medical management is apparent. No conclusion can be made at this time as to what treatment option, if any, is appropriate for UPCs.

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QUESTION 4: What is the role of quantitative evaluation (e.g., density of bacteria, cuti (propi) score) of positive cultures from the shoulder?

RECOMMENDATION: Semi-quantitative and quantitative reporting of bacterial culture results may have clinical utility for the diagnosis of shoulder periprosthetic joint infection (PJI) and may be used to interpret the relevance of positive cultures.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 0%, Abstain: 4% (Unanimous, Strongest Consensus)

RATIONALE

Introduction

Approaches to quantifying the bacterial load at the time of revision shoulder arthroplasty.

Infection is an especially problematic and potentially devastating complication of elective major joint arthroplasty. There is extensive recent interest in PJI of knee and hip arthroplasty leading to protocols for prevention, evaluation and management of PJI. Investigation of PJI of the shoulder has lagged in part due to the limited numbers of primary shoulder arthroplasty cases, the relatively infrequent recognition of PJI, and the difficulty in applying the traditional criteria for hip and knee PJI to the shoulder due to the issue of "stealth" presentation of *Propionibacterium,* frequently occurring at times long after the index procedure.

The diagnosis and management of a prosthetic joint infection is dependent upon identifying the pathogen. Prior to the recognition of *Cutibacterium* as a definite pathogen, it was not uncommon for cases of shoulder PJI to be unrecognized. More recent studies have attempted to determine the optimal approach to evaluation of potential shoulder PJI. This includes specific approaches to specimen harvest, culturing method and culture observation appropriate for identifying *Cutibacterium.*

While the results of a specimen culture are often reported as being "positive" or "negative," it is now apparent that the degree of positivity – that is the number of bacteria in the specimen – can vary widely. Quantitative cultures have been used by clinicians to estimate the threshold above which the bacterial burden will likely be of clinical significance [1]. Low levels of bacterial growth from a specimen may be of less clinical significance than high levels. In determining the clinical importance of any level of bacterial growth, it is also important to know the degree to which control specimens (i.e., a sterile sponge opened in the operating room (OR) without contact with the patient's tissue) demonstrate bacterial growth [2,3].

Quantitative culture results have been used to evaluate wound infection, urinary tract infections and bronchial brushings. In the case of urine the actual colony count of a urine specimen is necessary (one colony equals one colony-forming unit or CFU) and a positive culture with 100,000 CFU is considered to be indicative of a urinary tract infection [4]. A number of studies have investigated the relevance of bacterial count to wound healing. Bacterial counts above 10,000 to 100,000 are thought to be indicative of infection and delayed healing [5]. More recent work supports this concept but suggests that there is little to no benefit of quantitative biopsy analyses or quantitative wound surface cultures, with several studies finding a low correlation of culture to infection. The problem with any threshold, such as 100,000 CFU is that there can be no clinically significant difference between a count of 100,010 and 99,990.

Most standard bacterial cultures are evaluated using a semi-quantitative technique in which cultures are inoculated onto medium using a sterile loop that sequentially dilutes the specimen from the first area or quadrant of the medium to the last area or quadrant. Results are often reported as 1+, 2+, 3+ or 4+ (or as text, using such terms as "trace," "few," "moderate" or "abundant"), depending on which areas or quadrants demonstrate bacterial growth [1,6,7].

Bacterial load, the virulence of the organism, variations in host response and wound environment all may contribute to determining the effect of the bacteria in the wound. Despite this, the literature on shoulder PJI suggests wide variability in culture practice and rarely considers semi-quantitative or quantitative culture results [8]. The purpose of this systematic review was to identify information regarding quantitative evaluation of bacterial cultures and to relate this to the evaluation and management of shoulder PJI.

Methods

A Scopus search was performed with the query "(shoulder OR "upper extremity") AND (arthroplasty OR replacement OR revision) AND (culture OR microbiologic OR microbiology)." The resulting titles, abstracts and full text (127) from this query were reviewed for relevance to the question of number of samples for culture, specimen type and anatomic locations. All pertinent articles were then fully reviewed and any other pertinent citations in these gathered articles were obtained and reviewed. Based upon the findings of this review and review of the manuscript reference lists, an additional

search was performed on PubMed using the term "quantitative culture."

Results

The initial search identified 127 articles. After review of these articles, 11 were included in the final summary. Due to the nature of the available data, it was not possible to perform a meta-analysis. Thus, this is a narrative report of the findings.

Kallstrom, in a review article, discussed the role of quantitative cultures in determining if a nonhealing wound is infected [1]. Despite early work that emphasized the importance of quantitative wound tissue cultures, the current thought is that there is little to no benefit of quantitative biopsy analyses or quantitative wound surface cultures, with several studies finding a low correlation of culture to infection. Quantitative wound cultures of tissue is challenging, as the tissue must be accurately weighed, homogenized and serially diluted prior to inoculation of media for each dilution under aerobic and anaerobic conditions. Variations in biopsy collection processing and inoculation can often confuse the interpretation of quantitative wound culture results. The delay in reporting results from quantitative cultures makes clinical management difficult, so direct Gram staining has been used as a surrogate to determine bacterial loads in wounds. Early advocates of quantitative wound cultures were correct in realizing that clinical infection was influenced by an imbalance in the bacterial load, variations in the host response and wound type.

Ashan et al. studied a cohort of 137 patients who underwent revision shoulder arthroplasty and had at least one positive culture [6]. The subjects all had pain, stiffness or component loosening but did not have obvious clinical evidence of infection. The authors excluded subjects that did not have at least four culture specimens. The focus of the study was to use the semi-quantitative culture results to determine a measure of bacterial burden specific to *C. acnes*. They assigned numerical values (Specimen Propi Values) to the semi-quantitative Propionibacterium (now *Cutibacterium*) culture results: 0.1 (broth only), 0.1 (1 colony), 1, 2, 3, and 4 (1+, 2+, 3+, or 4+, respectively) and referred to this number as the "degree of positivity" for each specimen with the idea that this value "roughly" reflected the amount of bacterial growth [9]. They also calculated the sum for each type of specimen (humeral stem explant, humeral head explant, glenoid explant, collar membrane [between the modular head and stem], humeral membrane [between the humeral stem and humeral bone], other soft tissue, fluid, or "other") from each shoulder. The Specimen Propi Values for all of the specimens from a particular shoulder were summed to derive the Shoulder Propi Score for that shoulder. In order to account for the number of culture specimens in each case they calculated the Average Shoulder Propi Score, which they defined as the Shoulder Propi Score divided by the total number of specimens from that shoulder submitted for culture.

They reported that the average Specimen Propi Value for fluid (0.35 ± 0.89) was significantly lower than that for soft tissue (0.92 ± 1.50) and explant specimens (0.66 ± 0.90) ($p < 0.001$). Men had a significantly higher mean Shoulder Propi Score (3.56 ± 3.74) than women (1.22 ± 3.11) ($p < 0.001$), and men had a significantly higher Average Shoulder Propi Score (0.53 ± 0.51) than women (0.19 ± 0.43) ($p < 0.001$). Patient age did not have a significant effect on either score.

They further reported that, although the Shoulder Propi Score and Average Shoulder Propi Score varied among the shoulders that were culture-positive for Propionibacterium (now *Cutibacterium*), they could not identify a clear threshold above which they could be confident that a positive culture result represented a clinical infection, as opposed to contamination or commensal presence of an organism. The findings of this study clearly demonstrate that the identification of *C. acnes* is highly dependent upon the source of the culture specimen. The findings of this work have limitations, because the authors did not clearly determine what level of *C. acnes* burden constitutes a periprosthetic infection. Thus, true the value of semi-quantitative reporting of cultures is not clearly delineated. However, if one considers that the clinical manifestations of an infection are the result of an interaction between a host and a pathogen, then it is logical to consider that the amount of bacterial burden is important.

In a separate publication, Hsu and co-workers studied the results of epidermal, dermal and deep cultures obtained from subjects undergoing revision shoulder arthroplasty [7]. Based upon their data, they calculated that four different specimens would need to be cultured to have a 95% chance of detecting the organism and that, in order to achieve 95% of the positive cultures, the cultures need to be held for at least 14 days.

Carli et al. studied a mouse model of acute periprosthetic knee infection [10]. The experimental animals were inoculated with *S. aureus*. The infected animals demonstrated clinical signs of infection with impaired gait, implant loosening and elevated inflammatory markers. Viable *S. aureus* was quantified from the retrieved implant surfaces, and the infected animals had greater than 10^6 CFUs at 2 weeks and greater than 10^5 CFUs at 6 weeks.

Esteban et al. used quantitative culture analysis to study cases of PJI in which antibiotic loaded cement spacer was used during two-stage revision reconstruction [11]. Culture specimens were obtained from sonicated implants. Infection was defined by having one of the following criteria: (1) fistulae or wound dehiscence at the time of the second-stage surgery, (2) persistent pain around the joint associated with elevated C-reactive protein or (3) clinical appearance of infected tissue during surgery according to the surgeon. Thirteen of 50 specimens had positive sonicate cultures, 9 from infected cases and 4 from non-infected ones ($p = 0.001$, Fisher's exact test). The presence of high colony counts or a different isolate individually showed a strong statistical association with infection.

Grosso et al. studied implant sonication culture for the diagnosis of shoulder periprosthetic infection [12]. They defined infection according to their published guidelines that included four groups: definite infection, probable infection, probable contaminant or no evidence for infection. Their culture technique report quantified the number of CFUs for each specimen. Prior work by Trampuz et al. suggested that sonication fluid cultures of hip and knee arthroplasty implants had greater sensitivity than periprosthetic tissue cultures [13]. In contrast, Grosso et al. reported that there was no significant benefit to the shoulder implant sonication culture technique compared with standard intraoperative cultures. Using the cutoff value of > 20 CFU/mL to exclude contaminants, implant sonication culture had a low sensitivity (56%) but high specificity (93%). While without a cutoff value, implant sonication culture had a high sensitivity (96%) but low specificity (64%). Standard intraoperative cultures (tissue and fluid) had a better overall performance compared with the cutoff and non-cutoff sonication results.

Piper et al. also studied the role of sonication of shoulder implants and evaluated the relevance of quantitative reporting of the culture results [14]. In their previous work on hip and knee implants, they used a cutoff of 5 CFU per plate of sonicated fluid culture. In the study of shoulder implants they found that a cutoff of 20 CFU per plate with concentrated sonicate fluid resulted in a sensitivity and a specificity similar to those in their hip and knee work. In contrast to Grosso et al., they concluded that sonicate fluid culture is useful for diagnosing shoulder PJI.

Discussion

The clinical manifestations of an infection are the results of the interaction between a pathogen and the host. Kravitz wrote that "we

think of infection in terms of bioburden, which refers to the presence of bacteria in a wound and the number of microorganisms that contaminate an object" and subdivided bioburden into 4 categories: (1) contamination-bacteria within a wound without host reaction, (2) colonization-bacteria within the wound that multiply or initiate a host reaction, (3) critical colonization-bacteria that multiply to cause a delay in wound healing, often with increased pain but not with an acute host reaction and (4) infection-bacteria that multiply and cause a host reaction [15]. It seems logical that the presence of greater numbers of bacteria would correlate with the presence and severity of a periprosthetic shoulder infection. The results of this systematic review point out the paucity of available information, knowledge and understanding of the role of quantitative culture in the evaluation and management of shoulder PJI.

The limited data available suggests that standard fluid and tissue cultures are better than sonication cultures for diagnosis of shoulder PJI. However, there is insufficient experience and study of this technique to make definitive evidenced based recommendations. From a practical standpoint sonication is not readily available in all institutions. However, it seems that if sonication is used the quantitative culture results should reported.

New culture independent techniques and assays employed to identify the presence of bacteria including polymerase chain reaction, next generation sequencing and labeling techniques hold promise to aid both in the actual diagnosis of shoulder PJI as well as reduce the time to diagnosis. Nevertheless, the results of culture remain an important means to identify and characterize pathogenic microorganisms, to determine antibiotic susceptibility and to confirm the results of culture-independent methods. Previous experience demonstrates that the actual presence of bacteria does not always correlate with clinical manifestations of infection and that a number of pathogen and host factors must be considered in the diagnosis and management of shoulder PJI.

In summary, the results of prior studies in other specialties suggest that determining bacterial load with semi-quantitative and quantitative culture assessment in shoulder arthroplasty is of value in the evaluation and management of cases in which PJI is suspected. The application of these semi-quantitative and quantitative culture results to the evaluation of a failed shoulder arthroplasty requires (1) a standardized approach to harvesting specimens (source, number and technique), (2) using standardized culturing protocols designed to detect the presence of *Cutibacterium*, (3) standardized approach to reporting of the semi-quantitative or quantitative results and (4) documentation of the semi-quantitative or quantitative results of control specimens from the OR that have not been in contact with the patient.

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2.2. DIAGNOSIS: CULTURE TECHNIQUE

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QUESTION 1: What is the optimal culture technique (e.g., culture medium, days of incubation) in evaluating patients for shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: Current evidence suggests that culture of tissue samples for the diagnosis of shoulder PJI is best performed using both aerobic and anaerobic conditions. For solid culture media, diagnostic accuracy may be improved by using enrichment media. Fourteen days is the most common culture duration cited.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

PJI of the shoulder is a common indication for revision surgery [1]. The organisms that are most commonly responsible include *Staphylococcus* and *Cutibacterium acnes* (formally *Propionibacterium acnes*). Culture techniques and interpretation of culture results for the former are well established, but *C. acnes* is a ubiquitous skin commensal in humans. Therefore, the distinction between it being a contaminant versus pathogen is challenging. This is complicated by the fact that *C. acnes* is often associated with few local or systemic signs of inflammation and is often slow to grow in the laboratory. Defining the optimal culture technique for diagnosis of shoulder PJI is, therefore, important. However, even if this were achieved, cultures are likely to yield a proportion of false positive results, and, therefore, the inclusion of a confirmatory test in the diagnostic pathway is critically needed for the interpretation and corroboration of culture results. There are three main variables relating to culture conditions for the diagnosis of shoulder PJI.

Duration of Culture

In order to optimize detection of all organisms, including *C. acnes,* in upper limb PJI, most authors advise prolonged incubation, although the ideal duration has yet to be established. An incubation time which is too short may limit the sensitivity; an incubation time which is too long results in the isolation of non-diagnostic isolates or contaminants, thereby limiting the specificity.

Zappe et al. [2], in a retrospective analysis of 139 cases of PJI, suggest that *Cutibacterium* associated infection occurs at a frequency comparable to many other pathogens and that the median time to culture positivity is 8 days. They advise that tissue samples should be incubated for 14 days.

Schäfer et al. [3] likewise suggested that prolongation of the incubation period was associated with an increase in the proportion and diversity of positive samples. They recommended an incubation period of up to 14 days based especially on late recovery of aerobic gram-positive rods and *Cutibacterium* species.

Similarly, Butler-Wu et al. [4] estimated the median time to positivity using standard bacteriological methods to be 6 days with a range of 2-15.

Based on such studies, many authors advise a minimum incubation period of 14 days [5–8] while some advise at least 21 days [1,9].

However, prolonged incubation of cultures increases the risk of generating false positive results due to sample contamination and, therefore, may adversely affect the specificity of the test. A retrospective study by Frangiamore et al. [10] suggested that, amongst 46 cases, median time to *C. acnes* growth in the probable true-positive group was 5 days as compared to 9 days in the probable contaminant group ($p = 0.002$).

Peel et al. [11] demonstrated that, in 117 cases of proven PJI as defined by the Infectious Disease Society of America (IDSA) criteria, the median time to positivity using blood culture bottles was around 24 hours. Extending anaerobic incubation beyond 7 days yielded a diagnosis of PJI in only five additional subjects who fulfilled the IDSA diagnostic criteria and anaerobic blood culture bottles detected pathogen growth more rapidly than agar or thioglycolate broth.

Minassian et al. [12] prospectively analyzed 332 revision arthroplasty patients whose surgical samples were processed using both blood culture bottles and conventional media. Amongst 66 who had microbiologically confirmed PJI, 65 cases were identified as culture positive within 3 days and one at day 8.

Anaerobic and Aerobic Culture

PJI caused by strictly anaerobic pathogens is rare but mandates careful selection of antimicrobials for optimal therapy. While *C. acnes* is an anaerobic organism, many strains are aerotolerant and Butler-Wu et al. [4] suggested a significant and clinically important improvement in yield by using aerobic and anaerobic culture conditions. Peel et al. [11], however, suggest little advantage of prolonged aerobic cultures specifically for the diagnosis of *C. acnes* but reported benefit from extended anaerobic culture.

Choice of Culture Medium

Conventionally, the laboratory diagnosis of PJI has relied upon culture of tissue specimens on solid media (agar) and broth cultures. Unless they become visibly turbid, the latter are terminally subcultured onto agar to detect any non-visible growth in the broth. This is time consuming, cumbersome and provides no advantage over automated techniques.

Butler-Wu et al. [4] analyzed the accuracy of *C. acnes* PJI diagnosis in 198 revision arthroplasty procedures using four different culture media (blood agar, chocolate agar, Brucella agar and brain-heart infusion (BHI) broth). They found that recovery of *C. acnes* from blood agar was exclusively associated with the presence of infection (16 specimens), but all specimens positive for growth of *C. acnes* on blood agar were also positive for growth on at least one additional culture medium. BHI yielded the highest number false positive results and Brucella agar yielded the highest number of true positive results. They suggest that isolation of *C. acnes* from clinically proven infected cases were 6.3 times more likely to have two media positive for growth as compared to unproven cases of infection ($p = 0.002$).

Hughes et al. [13] prospectively compared conventional culture media and blood culture medium in 849 separate specimens from 178 patients undergoing arthroplasty revision. They estimated the sensitivity and specificity of blood culture medium to be 87% and 98% respectively. By comparison, the sensitivity of direct plates and cooked meat broth culture were 39% and 83%

Motwani et al. [14] found that, in 60 cases of pediatric septic arthritis caused by any organism, incubation of clinical samples in BACTEC blood culture bottles, as compared to conventional agar plates, increased the yield from 42% to 71%.

A prospective study of 369 adults by Peel et al. [11] similarly showed that use of blood culture bottles improved bacterial yield in comparison to conventional agar and broth culture (92.1% versus 62.6%, respectively).

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QUESTION 2: Should *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*) isolated in samples from the shoulder be sub-typed?

RECOMMENDATION: *Cutibacterium acnes* isolated in samples from the shoulder should not be routinely sub-typed.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The survey of the studies was conducted by searching PubMed since January 1, 2000 in the best match sort order with the following query ((Propionibacterium acnes OR Cutibacterium acnes OR P acnes)) AND (strain OR types OR typing OR phylogenetic OR orthopedic infection OR prosthetic joint OR arthroplasty OR shoulder OR implant OR instrumentation) AND (("2000/01/01"[PDat]: "3000/12/31"[PDat]) AND Humans[Mesh]).

Cutibacterium acnes (formerly known as *Propionibacterium acnes* [1]) is a member of the normal human skin microbiota and is associated with various infections and clinical conditions. It is frequently isolated from prosthetic joints (particularly shoulder arthroplasties) and the spine, mainly due to the proximity of these sites to areas of skin rich in pilosebaceous glands, where *C. acnes* reside [2,3].

C. acnes is one of the most frequent microorganisms isolated in shoulder periprosthetic joint infection (PJI). In contrast to the knee and hip joints, *C. acnes* has been isolated in 17.6% to 60% of periprosthetic shoulder infection cases [4–7]. However, its role in pathogenesis has been questioned [8], as up to 60% of patients that grow *C. acnes* from a prosthetic joint have no evidence of acute inflammation in histopathology [9]. Besides that, *C. acnes* has been present in culture specimens during primary shoulder surgery [10–12], and it has been identified as a common contaminant of the surgical field [13]. One possible explanation for these observations is that standard skin surface preparation cannot eliminate *C. acnes* in a high percentage of individuals, thus favoring inoculation from the more superficial dermal structures into the deep tissues during surgery [14].

Within the last 10 years, phylogenetic studies based on single and multilocus gene sequencing, as well as whole-genome analyses have provided valuable insights into the genetic population structure of *C. acnes*, particularly in the context of health and disease. The bacterium has an overall clonal structure, and its isolates can be classified into a number of phylogroups designated types IA1, IA2, IB, IC, II and III [15–17]. These types appear to display differences in associations with specific types of infections and vary in the production of putative virulence determinants, inflammatory potential, antibiotic resistances, aggregative properties and morphological characteristics. However, uncertainty still exists regarding the exact clinical relevance of these phylogroups, as well as the wider issue of whether isolates recovered from different clinical samples are truly representative of infection in all contexts or are simply skin contaminants or passive bystanders within a sample [15].

Since *C. acnes* can be isolated as a pathogen or a contaminant, it can be difficult to interpret clinical significance simply based on its isolation. In addition, subacute and chronic shoulder PJI typically present with low-grade, indolent clinical features and normal laboratory inflammatory markers, which further confounds this distinction [15–17]. Microbial characteristics that indicate whether the isolated *C. acnes* is a likely cause of orthopaedic implant infection versus a colonizing agent would be clinically useful. In a prospective study conducted by Sampedro et al. [18], the phylotype of *Cutibacterium* had no clear association with infection or colonization of failed orthopaedic implants [10]. To date, no clear association between phylotypes and infection/colonization or outcome of infection has been reported [13].

Considering this uncertainty over clinical relevance and utility and considering the high costs and limited availability in clinical microbiology laboratories, we suggest that *Cutibacterium acnes* isolated in samples from the shoulder should not be routinely specified according to phylogroups. Rather, these techniques should be reserved for research purposes. Studies focusing on the determination of phylotypes and identification of virulence factors associated with deep infection should be encouraged, since these tools may become useful to improve diagnosis by means of the development of new techniques to identify target strains that can cause infection [3].

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QUESTION 3: Is there a role for Polymerase chain reaction/next generation sequencing (PCR/NGS) technique in the diagnosis of shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: There is not sufficient data to support the use of PCR or NGS in diagnosis of shoulder PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive literature review was performed to identify all studies on use of PCR or NGS in diagnosis of shoulder PJI. Searches for the terms "polymerase chain reaction shoulder arthroplasty," "polymerase chain reaction shoulder replacement," "next generation sequencing shoulder arthroplasty" and "next generation sequencing shoulder replacement" were performed using the search engines PubMed and Scopus, which were searched through February 2018. Inclusion criteria for our systematic review were all English studies (Level I-IV evidence) that reported on PCR or NGS in diagnosis of shoulder PJI. Exclusion criteria were non-English language articles, nonhuman studies, retracted papers, case reports, review papers, studies with less than 10 patients in the sample size, studies without clinical follow-up/infection rates and technique papers without patient data. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed. After removal of duplicates, 12 titles were evaluated and zero studies met full inclusion and exclusion criteria to allow for analysis.

There is limited data in the shoulder literature specific to the use of PCR or NGS to diagnose periprosthetic joint infection. Holmes et al. won the Neer Award in 2017 for their investigation of a polymerase chain reaction-restriction fragment length polymorphism (RFLP) approach that sensitively and specifically identifies *C. acnes* in tissue specimens within a 24-hour period [1]. Samples from five surgical biopsies were tested with the PCR-RFLP assay, and samples from two patients undergoing revision shoulder arthroplasty for culture-positive *C. acnes* infection both yielded a positive result by PCR. Additionally, samples from 3 patients undergoing revision shoulder arthroplasty for aseptic indications tested negative with the PCR-RFLP assay. A recent study from the hip and knee arthroplasty literature demonstrated the potential for NGS to diagnose PJI. Tarabichi et al. performed a prospective evaluation of 65 revision hip and knee arthroplasties [2]. In 28 revisions, the cases were considered to be infected; cultures were positive in 17 cases (60.7%), and NGS was positive in 25 cases (89.3%), with concordance between NGS and culture in 15 cases. Among the 11 cases of culture-negative PJI, NGS was able to identify an organism in 9 cases (81.8%). This data indicates that NGS may provide additional information in cases of potential PJI. There is currently no published data on NGS in the shoulder. An unpublished study from the Rothman Institute indicates that some cases of monomicrobial shoulder PJI may have additional organisms that escape detection when culture is used, which may be detected by NGS. Further research will be needed to determine whether NGS has a role in shoulder PJI diagnosis.

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2.3. DIAGNOSIS: DIAGNOSTIC CRITERIA

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QUESTION 1: What clinical signs (e.g., gross wound changes (swelling, erythema or drainage)) are concerning for shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: The presence of a sinus tract is the only clinical sign that can be considered highly specific for shoulder PJI. Other clinical signs of shoulder PJI include unexpected wound drainage.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infections after shoulder arthroplasty often involve lower virulence bacteria such as *Cutibacterium acnes* and *Staphylococcus epidermidis*, and, as a consequence, the usual obvious signs of infection are frequently absent. In the case of subacute and late shoulder PJI (again, with inconsistently defined timing), the clinical presentation may be limited to a painful and stiff shoulder, which can lead to confusion with aseptic causes of prosthetic failure [1-3]. In these cases, clinical signs are not considered specific enough, and further investigations are needed for the diagnosis of infection.

A PubMed search was performed with the keywords "Shoulder" (Title) AND "Infection" (Title/Abstract). Among the 570 entries, we selected only the articles involving shoulder prostheses and focused on clinical studies only. We excluded the studies that did not report the initial presentation (one study focusing on the second stage of two-stage revision only). We found no meta-analysis reporting the initial clinical features at presentation. Twenty-five studies were included in the final full-text review for this analysis.

Among the 25 published series of shoulder periprosthetic infection, we identified in the literature [1–25], clinical symptoms were constantly cited as an important part of the diagnostic process. Despite this, clinical presentation was not always precisely reported in the published series [26], and this allowed only a limited analysis: 9 series did not give any information about clinical signs [2-4,7,15,18,21,22,25], and, in the 16 others, the clinical description was incomplete in most of the cases. Furthermore, the clinical criteria were never stratified by timing of presentation (acute, subacute, chronic), and, when they were, the definitions of these timings varied, making it impossible to draw conclusions regarding the utility of clinical features depending on timing of presentation.

Sinus Tract

The presence of a sinus tract has always been recognized among the major clinical criterion for the diagnosis of infection and is one of the criteria published by the Musculoskeletal Infection Society in 2009 [27]. Eleven of the 25 series reviewed reported on the presence or absence of a sinus tract at the time of diagnosis, accounting for 264 shoulders [5,9,10, 12-14,16,17,19,20,24]. A sinus tract was reported in 110 cases (41.7%). In each of these cases, infection was considered obvious, even in the absence of other clinical, laboratory (white blood cell count, C-reactive protein, erythrocyte sedimentation rate) or microbiological findings. In addition to a sinus tract formation, the development of unexpected wound drainage (drainage outside of the immediate postoperative period) is highly suspicious for the development of shoulder PJI. Kelly et al. [28] specifically utilized "wound drainage" in their definition of shoulder PJI. The inflammatory process leading to wound drainage from a previously dry, healing wound has limited etiologies and should significantly raise the suspicion for PJI.

Local Tissue Inflammation

The presence of erythema and swelling is mentioned in only 7 studies (187 shoulders) and reported in 71 cases (38%) [4,5,9,11,17,19,20]. Although very suggestive of infection, these symptoms are not usually considered specific enough to reach with certainty a diagnosis of infection. In fact, a certain degree of erythema and swelling can be seen in cases of hematoma, allergy or other acute aseptic problem (i.e., periprosthetic fracture or aseptic loosening).

Fever

Systemic signs of infection such as fever are rarely reported in association with shoulder PJI. Only 4 studies specified if fever was present at the time of diagnosis; 14 cases among 132 patients (10.6%) [14,16,19,20]. It is impossible to ascertain why fever was not reported in the other literature reviewed and whether it was not present or if it was an omission. The presence of fever in association with shoulder PJI suggests a more fulminant process. Fever in the absence of other clinical signs of shoulder infection may indicate another unrelated process.

Pain and Impaired Function

Although nonspecific, shoulder pain and dysfunction are the most frequent signs/symptoms associated with shoulder PJI. Shoulder arthroplasty, when performed for the proper indications,

is highly effective at pain relief. In many cases of late shoulder PJI, including those with unexpected positive cultures, a change in patient pain and dysfunction are often the only clinical manifestation. On the other hand, when pain does not normally diminish in the early recovery period after surgery (first few weeks), PJI should also be suspected. Two hundred fifty patients among 276 (90.6%) reported in 10 studies [1,5,6,8,10,14,19,20,23,24], suffered from shoulder pain and impairment at the time of diagnosis, making pain a sensitive symptom. Pain can be associated with other local signs (inflammatory wound, swelling, collection, fistula), or may be present in isolation. In the case of a painful shoulder arthroplasty, establishing a diagnosis of infection is often difficult and should be based on further investigation. Nevertheless, infection should be strongly considered in the case of a painful shoulder arthroplasty. In less than 10% of cases, an infected shoulder prosthesis can be painless, but in these cases, there is always local evidence for an infection (inflammatory wound, swelling, collection, fistula).

Stiffness

Limited range of motion is classically associated with shoulder periprosthetic infection, but was specifically reported in only one study (30 out of 44 patients; 68.2%) [5]. It frequently occurs in conjunction with pain, another nonspecific symptom.

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QUESTION 2: What radiographic findings are concerning for shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: Radiographic findings concerning for shoulder PJI include component loosening or migration, radiolucent lines, osteolysis, endosteal scalloping and new bone formation. Specifically, humeral loosening should significantly raise the suspicion for shoulder PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A formal comprehensive literature search was performed to address this subject. PubMed, conference proceedings and Google scholar were searched using the following terms and keywords: infection, periprosthetic, prosthesis, arthroplasty, low-grade, total shoulder, shoulder arthroplasty, radiology, X-rays and imaging.

Plain Radiographs

The typical clinical presentation of an acutely infected shoulder arthroplasty includes (1) local symptoms, such as shoulder pain, decreased range of motion, erythema, swelling, wound drainage, draining sinus, purulence and warmth; and (2) systemic symptoms, such as fever, chills and malaise and positive markers (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)). In the presence of these obvious signs of infection, any radiographic change will be attributed to periprosthetic shoulder infection (PSI). However, depending on the virulence of the infecting organisms and the intensity of the host immune response, an infected arthroplasty can have subtle or even no clinical signs. This is true of most subacute and chronic PSI and almost universally true in revision of cases of apparently aseptic failure that are subsequently determined to be infected. Plain radiographs may help to determine the diagnosis of PSI. If any of the following are present, infection should be considered: non-traumatic periprosthetic fracture, fracture of the arthroplasty material, implant loosening, osteolysis without loosening, periosteal new bone formation, subluxation due to cuff failure from infection or dislocation.

Detection of periprosthetic lucency, loosening of the prosthesis components, effusion, adjacent soft tissue gas or fluid collection, or periosteal new bone formation around the hip arthroplasty may suggest infection, but none are either sensitive or specific [1]. A study of 65 patients with painful hip arthroplasties found that the presence of either lucency or periosteal new bone formation was 75% sensitive but only 28% specific for diagnosis of PJI [2]. Periosteal new bone formation alone was 100% specific but occurred in only 16% of patients with PJI. Serial radiographs with progressively expanding lucency over several months may also suggest PJI.

Plain radiographs are essential for the evaluation of any painful shoulder arthroplasty but are neither sensitive nor specific for the diagnosis of low-grade indolent infection. Typical radiographic findings that suggest periprosthetic infection include radiolucent lines around the components, osteolysis, bone erosion, endosteal scalloping, new periosteal bone formation and shift of the components. These findings are, however, often absent in indolent or low-grade infection.

In a review of 193 revision shoulder arthroplasty patients without obvious clinical evidence of infection, Pottinger et al. [3] reported a 56% incidence of unexpected positive intraoperative culture, with *C. acnes* being identified most commonly in 69% of the positive cultures. They found that humeral component loosening and humeral osteolysis on plain radiographs were associated with 3-fold and 10-fold increases, respectively, in the risk of a positive *C. acnes* culture.

Radiolucent lines around the glenoid component have been reported to be common even in the immediate postoperative period [4–6]. Interpretation of these radiolucent lines in the absence of clinical symptoms or signs should be done with caution so as not to inappropriately assume that there is an infection. However, radiolucent lines that appear relatively early after surgery and those that are significant enough to cause loosening of the component should always raise a high index of suspicion of infection, especially in the presence of pain or stiffness.

Computed Tomography (CT) Scans

CT scans are often used in revision shoulder arthroplasty for evaluation of the remaining bone stock, implant position and loosening, glenoid component wear, soft tissue swelling, fluid collection, and rotator cuff tendon and muscle pathology. However, the value of CT scan as a direct diagnostic modality for infection is limited to the identification of the same structural changes as observed in plain radiographs, and the metal artifact from the implants can make the interpretation difficult.

If there is a need for computed tomography arthrography, such as for evaluation of rotator cuff integrity or glenoid loosening, a joint aspiration can be performed concomitantly for synovial fluid analysis and culture.

CT has the advantages of high spatial resolution and allows for the evaluation of signs of infection in the periprosthetic tissues. One study found that detection of joint distention upon CT imaging was highly sensitive (83%) and specific (96%) for suspected hip arthroplasty infection [2]. However, the added benefit of these findings beyond history, physical examination and plain radiographs is unclear. The same study found no difference in the evaluation of the bony structures compared to the use of plain radiographs.

Magnetic Resonance Imaging (MRI)

MRI is of little value in the diagnosis of infection because of metal artifact from implants and is seldom used. Adjustments in the image acquisition parameters can lessen but not eliminate these artifacts. The metal artifact reduction sequence (MARS) can be helpful is some occasions. The MARS technique allows visualization of structures adjacent to metal implants and may improve visualisation of periprosthetic bone and soft-tissue structures near total shoulder arthroplasty [7,8].

Nuclear imaging

Currently, little is known about the diagnostic accuracy of nuclear imaging for indolent or low-grade periprosthetic shoulder joint infection (PSJI). It is reported to have a limited direct role in diagnosis of lower extremity PJI [9,10].

Technetium Tc99m bone scintigraphy is sensitive for identifying a failed arthroplasty but cannot differentiate between infection and aseptic failure. Neither periprosthetic uptake patterns nor performance of the test as a 3-phase study significantly improves the accuracy, which is only about 50% to 70% [9].

Three-phase bone scintigraphy is one of the most widely utilized imaging techniques in the diagnosis of PJI. The intensity of uptake following injection of the radiopharmaceutical is measured at three different time points, corresponding to blood flow (immediate), blood pool (at 15 min) and late (at 2 to 4 h) time points [11,12]. Uptake at the prosthesis interfaces at the blood pool and late time points suggests PJI. A limitation of this technique is the lack of specificity.

Asymptomatic patients frequently have uptake detected by delayed-phase imaging in the first year or two after implantation [13]. Given that many PJI occur within this time period, this lack of specificity, reportedly as low as 18%, is a limitation for the use of this technology. However, three-phase bone scintigraphy may be more useful for PJI occurring late after arthroplasty.

A study of 92 patients undergoing evaluation for revision of hip arthroplasty at mean of 9 years after implantation found that increased uptake at both the second and third phases provided sensitivity and specificity for making an accurate diagnosis of 68% and 76%, respectively [14]. The fact that only a minority of these patients underwent revision limits comparison to a true diagnostic gold standard. Another study reported a sensitivity of 88% and a specificity of 90% for detecting PJI in 46 patients at a mean of 8.5 years after hip arthroplasty [15].

Other imaging modalities may be performed in conjunction with bone scintigraphy in an effort to increase specificity. Radioactive Indium (In111) is used to label autologous leukocytes, which are then re-injected with images being obtained 24 hours later. A positive scan is typically considered when there is uptake on the labeled leukocyte image, with absent or decreased uptake at the same location on the late-phase bone scan [16]. A late-phase bone scan combined with a 111In leukocyte scan was 64% sensitive and 70% specific for detection of PJI in 166 revision knee or hip arthroplasties at a median of 7 years after implantation [17].

Indium In 111-labeled white blood cell (WBC) scan has been regarded as the gold standard technique for diagnosis of infectious conditions that involve local accumulation of leucocytes (usually pyogenic organisms) [18]; however, the accuracy for PSJI is reported to be poor. In a study of 17 patients with verified PSJI, Strickland et al. [19] reported that 111In-labeled WBC count scan was obtained in eight shoulders and all scans were negative. Variable and often poor sensitivity and specificity of nuclear imaging in diagnosis of PSJI make the interpretation of the findings difficult [20].

Other studies using slightly different technologies have reported somewhat higher accuracies, with sensitivities ranging from 77 to 100% and specificities ranging from 86 to 91% [16,21,22]. Fluoro-2-deoxyglucose [^{18}F-FDG] positron emission tomography (FDG-PET) is widely used in cancer care and treatment and has emerged as a diagnostic modality for PJI. A meta-analysis of 11 studies involving 635 prosthetic hip and knee arthroplasties found that FDG-PET had pooled sensitivity and specificity values of 82.1% and 86.6%, respectively, for the diagnosis of PJI [23–27].

While several nuclear imaging techniques [28] have been used to diagnosis PJI, the most accurate and cost-effective technique has yet to be elucidated. Furthermore, with the high cost of performing and analyzing nuclear imaging, its role in the workup for PJI should be limited. As such, there is rare utility for nuclear imaging with the multitude of more cost-effective measures.

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QUESTION 3: What intraoperative findings are concerning for shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: The presence of humeral stem loosening and cloudy synovial fluid should raise suspicion for shoulder PJI. Gross intra-articular pus (without a mechanical or rheumatologic explanation) or the presence of a sinus tract, communicating with the implant, are pathognomonic for periprosthetic shoulder infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Each specific clinical question was queried via input of keywords into the PubMed search engine. Appropriate references were reviewed to summarize findings and determine the level of evidence. The bibliographies of selected articles were scanned for additional references that may be applicable to the question. The findings of applicable studies were synthesized to formulate recommendations.

Synovial Fluid Analysis

The presence of "cloudy" fluid noted intraoperatively is associated with *C. acnes* culture positive prosthetic shoulder revisions. When combined with other patient demographics (male), radiographic features (humeral osteolysis and glenoid loosening) and the presence of a humeral membrane, cloudy fluid was associated with a 3-6 fold increase in the risk of shoulder PJI [1,2]. The presence of cloudy fluid suggests an elevated white blood cell (WBC) count. However, what constitutes "cloudy fluid" is subjective. Additionally, the threshold value for an elevated WBC for shoulder PJI is unknown and may be lower than accepted levels for other prosthetic joint infections given the lower virulence of *C. acnes*. *C. acnes* infections have been associated with relative increases in lymphocytes and plasma cells rather than polymorphonuclear leukocyte (PMN) [3]. The currently accepted white blood cell count thresholds of > 1100-3000 cells/cc with a > 80% PMN differential for chronic hip and knee arthroplasty infections [4,5] are likely not relevant for the diagnosis of shoulder PJI due to the less vigorous inflammatory response elicited by common shoulder bacterial pathogens. However, given the potential for infection by bacterial species other than *C. acnes*, a synovial fluid WBC with differential is a potentially valuable initial screening test for shoulder PJI.

Gross Biofilm

There is weak evidence linking the presence of increased biofilm, specifically humeral membrane, to the presence of bacterial infection, notably *C. acnes* [1,2]. The presence of biofilm formation is common with bacterial infections and not specific to *C. acnes*. Humeral membrane can also be present in cases of aseptic humeral loosening. The amount of biofilm formation that would be considered pathologic or indicative of infection is subjective and not known.

Furthermore, biofilm formation present in infected cases may not be macroscopically detectable. The absence of increased biofilm visually does not rule out a bacterial infection. The presence of biofilm (membrane) alone does not accurately diagnose an infection but may be used as an adjunct finding.

Sinus Tract

See Shoulder: Section 2.3. Diagnosis: Diagnositic Criteria, Question 1 for discussion of sinus tract as diagnostic marker for PJI.

Humeral Stem Loosening

See Shoulder: Section 2.3. Diagnosis: Diagnostic Criteia, Question 5 for discussion of the association between humeral component loosening and PJI.

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QUESTION 4: What is the role for periprosthetic frozen section and permanent histology in evaluation of a shoulder arthroplasty for periprosthetic joint infection (PJI)?

RECOMMENDATION: Frozen sections or histology, reviewed by an experienced pathologist, may be useful in revision shoulder arthroplasty to evaluate for periprosthetic joint infection. The detection of infection with less virulent organisms, which make up a significant percentage of shoulder PJI, may be less reliable.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 95%, Disagree: 5%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Histologic analysis is well-established as a valuable tool for diagnosing lower extremity PJI [1–4]. Multiple studies of lower extremity revision arthroplasty have shown that frozen section has an accuracy in establishing PJI equivalent to that of permanent histologic analysis [2,5]. This led to the inclusion of frozen section in the American Academy of Orthopedic Surgeons (AAOS) clinical guidelines for the diagnosis of PJI [6], the Musculoskeletal Infection Society (MSIS) definition of PJI [7], and the first International Consensus Meeting on Periprosthetic Joint Infection definition of PJI in 2013 [8].

Intraoperative assessment of periprosthetic inflammation can serve as a quickly available tool in the evaluation for PJI. Despite the extensive evidence supporting its utility in the evaluation of lower extremity arthroplasty, the literature on histologic analysis in shoulder arthroplasty is very limited. Because *Cutibacterium acnes*, a less virulent pathogen, is the predominant cause of shoulder PJI a reassessment of standard markers for PJI is necessary [9–12]. For this purpose, a systematic review of histologic analysis for shoulder PJI was undertaken on Scopus [13] with the query, "(shoulder OR 'upper extremity') AND (arthroplasty OR replacement) AND (infection OR infected) AND ('frozen section' OR histology OR histologic)."

This query identified two articles directly evaluating the use of frozen section in revision shoulder arthroplasty [14,15]. First, Topolski et al. [15] evaluated the utility of frozen section histopathology in patients with unexpected positive cultures (UPC) during revision shoulder arthroplasty. In 75 patients undergoing revision shoulder arthroplasty who had occult infection defined as positive intraoperative cultures, 92% (67/73) had a negative result on frozen section—with a positive result defined as at least five neutrophils on any high-powered field. In this study, there was a single case with a discrepancy between frozen section (negative) and permanent histology (positive). This study demonstrated that most patients with unexpected positive cultures did not have a strong periprosthetic inflammatory response. They concluded that frozen section analysis was not helpful in cases of UPC when using the criteria of Mirra et al. [16].

The second study, Grosso et al., evaluated the results of frozen section in forty-five revision total shoulder arthroplasties [14]. Based upon their definition for infection, the cohort was divided into non-infected (n = 15), infected (n = 12), and *C. acnes* infection (n = 18). Using the threshold from Moraweitz et al. [17], 23 neutrophils over five high-powered fields, frozen section had sensitivity and specificity of 67% and 100% for the infected group and 56% and 100%, respectively, for the *C. acnes* group. Re-evaluating the threshold for positive frozen section with a receiver operating characteristic (ROC) curve found that five high powered fields with a sum of at least ten neutrophils improved the overall sensitivity to 73% without sacrificing specificity. At that institution, with the aid of an experienced pathologist, these authors were able to demonstrate that a lowered threshold for these less-virulent infections can improve the accuracy and utility of frozen section analysis for diagnosing PJI during revision shoulder arthroplasty.

While these two studies are the only shoulder-specific analyses of frozen section for shoulder PJI, their developed thresholds have not been widely adopted by clinical pathologists. In fact, one of the two institutions noted above has since abandoned the clinical use of their published criteria. Therefore, utilization of the standard thresholds from the lower extremity arthroplasty community may be the most prudent currently.

Multiple studies of histologic analysis during lower extremity revision arthroplasty have demonstrated that the concordance between frozen section and permanent histology is very high. Thus, it is expected that the same difficulties with detection of infection by less virulent organisms in shoulder PJI would apply to both permanent, as well as frozen section, histology [2,5,18].

Histologic analysis is also used to evaluate for persistent infection during reimplantation of a hip or knee undergoing two-stage exchange [19–21]. These analyses found poor sensitivity but high specificity in identifying persistent PJI. Such analysis has not been completed in the shoulder and further work is required in this regard.

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QUESTION 5: What are the diagnostic criteria of shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: See International Consensus Meeting (ICM) definition of shoulder PJI below.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 88%, Disagree: 12%, Abstain: 0% (Super Majority, Strong Consensus)

INTERNATIONAL CONSENSUS MEETING (ICM) FOR PERIPROSTHETIC JOINT INFECTION: DEFINITION, CATEGORIZATION AND SCORING SYSTEM FOR SHOULDER PJI

Definite PJI

Meeting one of the following criteria is diagnostic of **definite** periprosthetic shoulder infection:

- A sinus tract communicating with the prosthesis is present
- Gross intra-articular pus
- Two positive cultures with phenotypically-identical virulent organisms

Evaluation Scoring

Weighted values for all positive tests performed as part of the diagnostic evaluation of a failed shoulder arthroplasty are summed (Table 1).

- Six or greater with identified organism = **probable PJI**
- Six or greater *without* identified organism = **possible PJI**
- Six or less
  - single positive culture virulent organism = **possible PJI**
  - two positive cultures low-virulence organism = **possible PJI**
  - negative cultures or only single positive culture for low virulent organism = **PJI unlikely**

RATIONALE

The need for a consensus definition of shoulder PJI cannot be understated. A clear definition serves two purposes: (1) to aid in clinical decision making and (2) to provide a framework for consistent future research reporting. Furthermore, acceptance of a definition is a necessary first step in providing a well-tested diagnostic algorithm. As Hsu et al. demonstrated [1], the shoulder research community has used disparate definitions of PJI—likely leading to variable and inconsistent conclusions about the diagnosis and management. Adoption of a uniform definition of PJI for the lower extremity quickly led to hundreds of publications evaluating prevention, diagnosis and treatment of PJI based upon the same consistent diagnostic criteria [2,3]. This task is even more urgent in regard to shoulder arthroplasty due to the unique microbiologic and the ambiguity presented by high rates of positive intraoperative cultures in revision cases that otherwise appear aseptic [4–9]. In order to discuss diagnosis and evaluation of shoulder PJI, it is imperative that the shoulder community begin with a standardized and accepted definition of shoulder PJI.

TABLE 1. Weighted values for all positive tests performed as part of the diagnostic evaluation of a failed shoulder arthroplasty

Minor Criteria	Weight
Unexpected wound drainage	4
Single positive tissue culture (virulent organism)	3
Single positive tissue culture (low-virulence organism)	1
Second positive tissue culture (identical low-virulence organism)	3
Humeral loosening	3
Positive frozen section (5 PMN in at least 5 high-power fields)	3
Positive preoperative aspirate culture (low or high-virulence)	3
Elevated synovial neutrophil percentage (> 80%)*	2
Elevated Synovial WBC (> 3,000 cells / µL)*	2
Elevated ESR (> 30 mm/hr)*	2
Elevated CRP (> 10 mg/L)*	2
Elevated synovial alpha-defensin	2
Cloudy fluid	2

PMN, polymorphonuclear leukocyte; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein
*Beyond six weeks from recent surgery

Committee Goals

1. Define criteria that establish a diagnosis of shoulder PJI.
2. Provide a common language for research reporting and clinical decision making.
3. The definition should be flexible enough to include the "obvious" suppurative, shoulder PJI, as well as the subtler "stealth" infections and cases where the clinical scenario is unclear.
4. Incorporate the best available evidence in this field.
5. That the definition of shoulder PJI should generally be similar to the Musculoskeletal Infection Society (MSIS) hip and knee definition, but differ according to specific characteristics unique to the shoulder.
    a. Less weight put on positive cultures with low-virulence organisms given the data on this phenomenon in the shoulder.
    b. A larger "grey area" of "possible PJI" to recognize that there are a large number of cases where, given the current state of the field, it is not possible to define as clearly infected or uninfected.
    c. Include a scoring system in order to potentially create objective criteria for sorting these "possible PJI" cases.

Committee Process

The process undertaken to formulate this definition was a consensus effort relying upon the clinical expertise of numerous shoulder and elbow surgeons who routinely treat shoulder periprosthetic joint infection. First, a systematic review as undertaken to evaluate the definitions in use for shoulder PJI and the evidence for each (this is included in Appendix A). Second, over a year-long process, the 69 ICM delegates (experts in shoulder PJI and infectious disease from 11 countries) performed 75 separate, parallel systematic reviews evaluating aspects of prevention, diagnosis and management of shoulder PJI. Following a Delphi process these reviews were disseminated, discussed and then refined in-person at the Second ICM in Philadelphia (July 2018) where delegates voted on each statement. Each of these 75 reports was used by the definition committee in addition to their own experience to discuss potential definition options. These were refined, voted upon and ultimately accepted at the ICM meeting in Philadelphia. The original MSIS criteria have gone through multiple iterations as the consensus definition has been refined through testing and further research. The definition of shoulder PJI is no different, and we fully expect that as researchers begin to adopt this definition the criteria and weightings may change, as our knowledge and understanding of the evaluation and management of shoulder PJI evolves.

Rationale for the Definition

While there remains controversy and uncertainty about the definition and management of shoulder PJI, there are cases that are considered to be unquestionably infected. Therefore, a subgroup of "Definite PJI" shoulder PJI was defined to identify these cases. This included the presence of a sinus tract (as discussed Section 2:3, Question 1), gross intra-articular pus, or two separate positive cultures with identical virulent pathogens (as discussed in Section 2:1, Question 1). While specific evidence for these criteria is lacking, a strong consensus existed that if any of these criteria were met, an infection was undoubtedly present. When assessing intra-articular purulence, consideration must be given to other less common inflammatory conditions, including rheumatologic disease and

reactions to metal or other foreign bodies, which rarely incite a process that produces debris or aseptic purulence in shoulder arthroplasty.

As discussed in Section 2:1, Question 1 and Section 2:5, Question 8, the significance of a positive culture may depend upon the number of cultures sent and the degree of growth. Therefore, as discussed in "Diagnosis: Sampling" Question 8, it is recommended that "five deep tissue specimens for culture be obtained from various surgical sites (e.g., capsule, humeral canal, and periprosthetic membranes in the proximal humerus and glenoid)." This should provide sufficient sensitivity for bacterial growth while minimizing the risk of false positives, as discussed in Section 2:1, Question 1. Furthermore, when reporting results we recommend that the number of positive cultures should be reported as a fraction of the total cultures sent (x/y where x = number of positive cultures and y = total number of cultures sampled) and/or the "Shoulder propi score" Section 2:1, Question 2). Lastly, as discussed in Section 2:2, Question 1, cultures should be held for fourteen days to optimize detection of pathogens.

The lack of these defining signs certainly does not exclude the diagnosis of PJI. Therefore, in these less distinct scenarios three categories were established: "Probable PJI," "Possible PJI" and "PJI unlikely." Given the lack of strong evidence defining the clinical significance of low-virulence positive cultures, this stratification allows for clinical guidance and classification of cases for research purposes without grouping heterogenous cases. For classification of these cases, minor criteria were proposed and edited by the group at large. Many of these minor criteria have been discussed in other questions (Table 1). As the significance of a positive result for these minor criteria varies, each criterion was weighted. It was agreed that a threshold score of six would serve as a marker of the increased likelihood of a shoulder PJI, though the committee fully expects that as this definition is tested and refined, the weightings and the thresholds will be improved.

To apply weight for each of these minor criteria, a score was applied to each criterion independently by every member of the shoulder group in attendance. These scores were then averaged and discussed further, resulting in the weighting reported here. To further test the definition, clinical scenarios were proposed and evaluated with the definition (Table 2). In each case, the ICM diagnostic criteria gave a result which the delegates felt, with consensus, described their own clinical conclusions.

Inflammatory markers (synovial fluid white blood cell count and differential, serum erythrocyte sedimentation rate, and serum C-reactive protein) are often elevated during the early postoperative period, and, thus, use in the diagnostic evaluation was limited to beyond six weeks from a recent surgery. There have been multiple studies in the lower extremity demonstrating the impact of surgery on these inflammatory markers [10,11]. Normal thresholds for inflammatory markers in the acute postoperative period after shoulder arthroplasty have not been established.

The formation of this definition provides an important step in improving the care for patients with and understanding of shoulder PJI. Adoption of this definition by those performing research of shoulder PJI will allow for uniform evaluation of study outcomes as researchers, reviewers and readers will all be using the same language. Lastly, we want to emphasize this definition is a first iteration. As the understanding of shoulder PJI evolves and each diagnostic test is further evaluated, it will be necessary to revisit this definition as a community.

APPENDIX A

Search Strategy and Study Selection

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we conducted a systematic review to identify all studies concerning diagnosis and treat-

TABLE 2. ICM questions discussing each minor criterion in greater detail

Minor Criteria	Question
Unexpected wound drainage	Section 2:3, Question 1
Single positive tissue culture (virulent organism)	Section 2:1, Question 1
Single positive tissue culture (low-virulence organism)	Section 2:1, Question 1
Second positive tissue culture (identical low-virulence organism)	Section 2:1, Question 1
Humeral loosening	Section 2:3, Question 2
Positive frozen section (5 PMN in at least 5 high-power fields)	Section 2:3, Question 4
Positive preoperative aspirate culture (low or high-virulence)	Section 2:5, Question 8 Section 2:4, Question 9
Elevated synovial neutrophil percentage (> 80%)	Section 2:4, Question 3
Elevated Synovial WBC (> 3,000 cells / µL)	Section 2:4, Question 3
Elevated ESR (> 30 mm/hr)	Section 2:4,Question 1
Elevated CRP (> 10 mg/L)	Section 2:4, Question 1
Elevated synovial alpha-defensin	Section 2:4, Question 7
Cloudy fluid	Section 2:3, Question 3

PMN, polymorphonuclear leukocyte; WBC, white blood cell; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein

TABLE 3. Clinical scenarios of the ICM diagnostic criteria in practice

#	Scenario	Definition
1	Painful shoulder arthroplasty: • Positive aspirate culture (*C. acnes*): 3 points • 1/5 intraoperative cultures positive (*C. acnes*): 1 point • Humeral loosening: 3 points	Probable PJI
2	Painful shoulder arthroplasty: • No aspirate completed • Persistent unexpected wound drainage: 4 points • 2/5 intraoperative cultures positive (*C. acnes*): 1 + 3 = 4 points	Probable PJI
3	Painful shoulder arthroplasty: • Dry aspirate • 2/5 intraoperative cultures positive (MSSA) • Elevated ESR • Elevated CRP	Definite PJI
4	Painful shoulder arthroplasty: • Well-fixed components • 2/5 intraoperative cultures positive (*C. acnes*): 1 + 3 = 4 points • All other tests negative	Possible PJI
5	Painful shoulder arthroplasty: • Persistent unexpected wound drainage: 4 points • 1/5 intraoperative cultures positive (*C. acnes*): 1 point • All other tests negative	Unlikely PJI
6	Painful shoulder arthroplasty: • Persistent unexpected wound drainage: 4 points • 1/5 intraoperative cultures positive (MSSA): 3 point • All other tests negative	Probable PJI

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MSSA, methicillin-sensitive *S. aureus*

ment of "infection" at the time of revision shoulder arthroplasty. We searched for all studies published in English using the terms (("revision" OR "failed") AND "shoulder" AND ("arthroplasty" OR "replacement")) limited to dates between January 1, 1996 and February 3, 2018.

A total of 2,354 studies were identified. We reviewed the titles and abstracts of all studies and excluded studies that (1) included patients with shoulder infection without arthroplasty, (2) reported on patients with positive cultures not considered infection or that were "unexpected," as a strict definition of infection in these studies was not applied, or (3) included patients with arthroplasty of joints other than the shoulder. The reference lists for all included studies were searched for any additional references and three references were added to our list. A total of 25 studies met inclusion criteria and were included in the final analysis.

Data Collection

Relevant data were extracted from the selected publications, including the definition of infection used by the authors and the components it involved. Factors involved in the definition of infection included (1) clinical symptoms (erythema, sinus tract formation, drainage, systemic symptoms), (2) preoperative laboratory serology, (3) radiologic tests for infection, (4) preoperative aspiration laboratory results, (5) preoperative aspiration culture results, (6) intraoperative frozen section results and (7) intraoperative culture results.

Results

See Appendix A, Table 1 below. An explicit statement describing how infection was defined was not present in 6 of 25 studies. A classification system was used in 5 of 25 of the studies, including three that utilized the Musculoskeletal Infection Society definition described by Parvizi et al. [2], one that utilized a definition reported by Spangehl et al. [12] for total hip arthroplasty, and one that utilized the classification described by Grosso et al. [13]. The remaining 14 studies used author-defined combinations of clinical symptoms, laboratory tests, radiographic characteristics, findings on aspiration, and results of cultures of specimens harvested at the time of revision.

Workup for Periprosthetic Infection

Utilization of clinical signs and symptoms, preoperative serology, radiographic loosening and preoperative aspiration to workup and define infection was highly variable in the studies reviewed (Table 1). Of the 19 studies that provided a definition for infection, all used clinical examination findings as part of their definition, 14 used serum laboratory results, 6 utilized preoperative shoulder joint aspirate laboratory values, 10 used an intraoperative gram stain or frozen section and 6 used radiographic findings to aid in diagnosis. While all studies performed either preoperative aspiration or intraoperative tissue sampling for culture, intraoperative culture results were utilized in the definition of infection in only 10 studies.

APPENDIX A: TABLE 1. Definition of infection in included studies

Author	Year	Definition Provided	Clinical Exam	Serum Lab Values	Aspirate Values	Aspirate Culture	Surgical Specimen Culture	Intraoperative Frozen / Gram Stain	Radiographic Findings
Previously described criteria									
Ghijselings [14]	2013	"criteria proposed by Parvizi et al."	✓	✓	✓	✓	✓	✓	X
Grubhofer [15]	2018	"according to the Musculoskeletal Infection Society (MSIS) PJI criteria"	✓	✓	✓	✓	✓	✓	X
Jacquot [16]	2015	"according to the Musculoskeletal Infection Society criteria"	✓	✓	✓	✓	✓	✓	X
Lee [17]	2017	"probable or definite infection as the criteria for periprosthetic shoulder infection [by Grosso et al.]"	✓	X	X	X	✓	✓	X
Romanò [18]	2012	"criteria established by Spangehl et al."	✓	✓	X	✓	✓	✓	X
Combined definition									
Achermann [19]	2013	"(1) visible purulence of a preoperative aspirate or intraoperative periprosthetic tissue, (2) presence of a sinus tract communicating with the prosthesis, (3) microbial growth in a preoperative joint aspirate, intraoperative periprosthetic tissue or sonication fluid of the removed implant, or (4) synovial fluid with > 1,700 leukocytes/ul or > 65% granulocytes."	✓	X	✓	✓	✓	X	X
Amaravathi [20]	2012	"based on a combination of symptoms, laboratory tests, and findings of physical examinations such as draining sinus, radiological evidence of loosening of prosthesis, and analysis of intraoperative specimen."	✓	✓	X	X	✓	X	✓
Beekman [21]	2010	"clinical picture… swelling, redness, or a sinus… and laboratory tests… or fistula without altered laboratory tests"	✓	✓	X	X	X	X	X
Buchalter [22]	2017	"clinical, laboratory, radiographic, and operative evaluations"	✓	✓	X	✓	X	✓	✓

TABLE 1. Definition of infection in included studies (*Cont.*)

Author	Year	Definition Provided	Clinical Exam	Serum Lab Values	Aspirate Values	Aspirate Culture	Surgical Specimen Culture	Intraoperative Frozen / Gram Stain	Radiographic Findings
Coste [23]	2004	"1) the presence of a sinus; 2) serum leucocyte count; 3) erythrocyte sedimentation rate; 4) C-reactive protein (CRP); 5) preoperative and peroperative joint aspiration cultures and cultures of surgical specimens; 6) loosening of the components on standard radiographs and periosteal reaction; and 7) three-phase bone isotope scanning."	✓	✓	X	✓	✓	X	✓
Jawa [24]	2011	"combination of symptoms, physical findings, and laboratory tests"	✓	✓	X	X	X	X	X
Jerosch [25]	2003	"clinical symptoms associated with positive blood tests… intra-articular aspirates with WBC over 30,000 cells or positive bacterial growth"	✓	✓	✓	✓	X	X	X
Kelly [6]	2009	"associated skin erythema, wound drainage, or obvious purulence or tissue synovitis at the time of surgery… clinical aspiration yielding a positive Gram stain or culture was considered infected… positive intraoperative Gram stain or frozen section showing more than five polymorphonuclear leukocytes per high-powered field was considered infected."	✓	X	X	✓	✓	✓	X
Levy [26]	2015	"clinical evaluation, radiographs, and laboratory test results"	✓	✓	X	X	X	X	✓
Mahure [27]	2016	"combination of clinical, radiographic, and laboratory tests"	✓	✓	✓	✓	X	✓	✓
Sabesan [28]	2011	"clinical suspicion, positive intraoperative frozen sections, positive culture treated at an outside referring institution, positive preoperative aspiration cultures, or positive intraoperative tissue cultures"	✓	X	X	✓	✓	✓	X
Sperling [29]	2001	"patient's clinical course, the observation of purulence at the time of surgery, and a sinus that communicated directly with the joint"	✓	X	X	X	X	X	X

TABLE 1. Definition of infection in included studies (*Cont.*)

Author	Year	Definition Provided	Clinical Exam	Serum Lab Values	Aspirate Values	Aspirate Culture	Surgical Specimen Culture	Intraoperative Frozen / Gram Stain	Radiographic Findings
Stone [30]	2017	"history of previous infection, findings on physical examination (i.e., skin erythema, swelling, draining sinus), laboratory tests (white blood cell count, erythrocyte sedimentation rate, and C-reactive protein) when obtained, and positive intraoperative findings, including purulence, intraoperative frozen section showing more than 5 polymorphonuclear leukocytes per high-powered field for 5 fields, and cultures"	✓	✓	X	X	✓	✓	X
Weber [31]	2011	"...to substantiate the clinical suspicion, laboratory analysis and radiological examination with blood tests including CRP and WBC. In patients with fistula, microbiological swabs were taken before the procedure and in other patients the joint itself was aspirated. In the case of remaining doubt about the infection, an indium-labelled white blood cell scan was performed."	✓	✓	X	✓	X	X	✓
No clear definition provided									
Braman [32]	2006	"No objective grading criteria were used."							
Ince [33]	2005	None							
Klatte [34]	2013	None							
Ortmaier [35]	2014	None							
Strickland [36]	2008	No explicit definition							
Zavala [37]	2012	None							
Overall	✓= Component of definition		19	14	6	12	11	10	6
	X = Not considered		0	5	13	7	8	9	13

This search methodology, results and table have been adopted and updated from Hsu et al. [1].
CRP, C-reactive protein; MSIS, Musculoskeletal Infection Society; PJI, periprosthetic joint infection; WBC, white blood cell

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2.4. DIAGNOSIS: INFLAMMATORY MARKERS

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QUESTION 1: What is the role for serum erythrocyte sediment rate (ESR), C-reactive protein (CRP), or white blood cell (WBC) count in the evaluation of a shoulder arthroplasty for periprosthetic joint infection (PJI)?

RECOMMENDATION: Serum ESR, CRP or WBC count have poor sensitivity for the diagnosis of shoulder PJI. Although they should be obtained as part of a standard workup for infection, normal values do not rule out infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive literature search for periprosthetic shoulder infection was performed of the PubMed/Medline, Cochrane, Google Scholar and Embase databases through February 2018. The search terms used were "periprosthetic joint infection," "revision shoulder arthroplasty," "CRP," "ESR," "WBC." The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was followed for this review. Studies (Level II-IV evidence) in which at least one of ESR, CRP and WBC count were recorded in patients with periprosthetic shoulder infection or in patients with positive intraoperative culture were included in the study. Exclusion criteria were case reports, studies on non-prosthetic shoulder implants, studies with missing patient data, papers where the cutoff value is not specified for ESR, CRP and WBC, and non-English language papers.

The diagnosis and the treatment of shoulder PJI can be difficult [1,2]. *Cutibacterium acnes*, which causes indolent infection, is the most common causative agent of shoulder PJI [3–5]. In the case of infection caused by this agent that has low virulence, inflammatory markers such as ESR, CRP and WBC, are generally not elevated [6]. On the other hand, immunosuppression secondary to rheumatoid arthritis or systemic lupus erythematosus is the leading cause of the increased risk of infection in this group of patients [7]. The presence of high CRP and ESR values in the natural course of these diseases may lead to confusion in interpreting these parameters in terms of infection.

There is a paucity of literature regarding serum ESR, CRP or WBC count in the evaluation of a shoulder arthroplasty for PJI [3,8]. The most comprehensive meta-analysis regarding laboratory parameters in shoulder periprosthetic infection was performed by Nelson et al. [8]. The authors reported a mean ESR of 27.6 mm/h (in 231 patients), a mean WBC count of 7472 cells/μL (in 418 patients) and a mean CRP of 2.6 mg/dL (in 279 patients). Only 6.8% of patients who were treated for shoulder PJI had an elevated WBC, 37.6% of the patients had an elevated CRP while elevated ESR was reported in 62.1% of the patients (Table 1).

Whereas in the series of Pottinger et al. [9], these values were reported to be 8%, 20%, and 17%, respectively. In a study by Topolski et al. [3], it has been reported that 93% had a normal WBC count, 86% had a normal ESR and 75% had a normal CRP level.

The limited literature focuses on the sensitivity and specificity of laboratory tests [1,10–12]. Berbari et al. [10] reported sensitivities of ESR and CRP of only 16% and 42% in the shoulder, and 75% and 88% in the lower extremity, respectively. A few authors reported that the sensitivity of ESR was 12-45% and the specificity was 65-98% in detecting shoulder PJI [1,11,12]. For CRP, the sensitivity was reported as 0-46% and the specificity as 84-95%. Due to considerable heterogeneity, those indexes were not deemed suitable to be pooled (I^2 for the sensitivity of CRP was 97.7% and for the sensitivity of ESR was 91.5%).

In a majority of the studies, WBC was normal and CRP was usually increased in the shoulder PJI [3,5,13]. Piper et al. [1] have investigated the role of CRP and ESR in shoulder PJI since CRP and ESR are a useful diagnostic tool for knee and hip PJI. According to this, they stated that CRP was an effective parameter in distinguishing aseptic failure and infection of shoulder arthroplasty, whereas ESR was not. In the diagnosis of the shoulder PJI, while a CRP > 10 mg/L had a sensitivity of 42% and specificity of 84%, an ESR > 30 mm/h had a sensitivity of 16% and specificity of 98%.

Recently, optimized cutoff values of CRP and ESR for shoulder PJI have been published [1]. Optimized ESR cutoff for shoulder arthroplasty was 26 mm/h. This ESR cutoff value had a sensitivity of 32% and specificity of 93% for the shoulder PJI. Optimized CRP cutoff was 7 mg/L, and this value had a sensitivity of 63% and specificity of 73% for the shoulder PJI [1].

In a retrospective study using national insurance database by Chalmers et al., laboratory tests to diagnose infection in the setting of revision shoulder arthroplasty have been examined. In that study involving 1392 patients, the best diagnostic performance was attributed to the combination of ESR, CRP, and WBC (sensitivity = 7-42%, specificity = 92%, positive predictive value = 45%, negative predictive value = 91%, accuracy = 84-85%).[14]

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TABLE 1. Mean values and rates of elevation in ESR, CRP and WBC values in the study by Nelson et al.

	Number	Mean Values	Rates of Elevation
ESR	231	27.6 mm/h	62.1%
CRP	279	2.6 mg/dL	37.6%
WBC	418	7,472 cells /μL	6.8%

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC, white blood cell

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QUESTION 2: Is there a role for (a) synovial or (b) serum IL-6 in the diagnosis of shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: (a) There is a potential role for synovial fluid IL-6 in the diagnosis of shoulder PJI, both as an individual marker and when interpreted in combination with other synovial fluid markers. (b) Although its specificity is high, serum IL-6 does not appear to provide additional information beyond the more readily available serum markers (erythrocyte sedimentation rate (ESR), C-reative protein (CRP), white blood cell (WBC) count).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 0%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

(a) Synovial

Several meta-analyses [1,2] have been performed on synovial biomarkers in the hip and knee PJI literature, with multiple markers showing very good diagnostic test characteristics, including synovial interleukin (IL)-6. Lee et al. [1] found that the sensitivity, specificity, diagnostic odds ratio (DOR) and area under the curve (AUC) for synovial IL-6 was 0.81, 0.94, 4.38, and 0.95, respectively, in one of these recent meta-analyses. The results for studies specifically of shoulder PJI are also very promising,[3,4] but with diagnostic test performance that is slightly lower compared to the hip and knee findings, likely due to the indolent nature and lower virulence of the common infecting organisms in the shoulder, *Cutibacterium acnes* (*C. acnes*) and coagulase-negative *Staphylococcus* species (CNSS).

Frangiamore et al. [3] prospectively examined intraoperative levels of synovial IL-6 in 35 cases of revision shoulder arthroplasty; 15 cases categorized as infected and 20 as not infected based on perioperative criteria (Table 1). Using a cut-off level of 359.3 pg/mL based on ROC analysis, synovial fluid IL-6 was found to have an AUC of 0.891, with a high sensitivity (87%) and high specificity (90%) and a positive

TABLE 1. Periprosthetic shoulder infection criteria

Category	Criteria
Definite Infection	At least 1 positive preoperative or intraoperative finding of infection* and more than 1 positive culture (preoperative or intraoperative) *or* One positive preoperative culture (aspirate) and 1 positive intraoperative culture with the same organism
Probable Infection	At least 1 positive preoperative or intraoperative finding of infection* and one positive culture (preoperative or intraoperative *or* No preoperative or intraoperative findings of infection* and more than one positive culture (preoperative or intraoperative)
Probably Contaminant	No preoperative or intraoperative findings of infection* and one positive culture (preoperative or intraoperative)
No Evidence for Infection	No preoperative or intraoperative findings of infection* and no positive cultures (preoperative or intraoperative)

*Preoperative or intraoperative findings of infection:
- Preoperative clinical signs (swelling, sinus tract, redness, drainage).
- Positive result on serum erythrocyte sedimentation rate or C-reactive protein analysis. Intraoperative gross findings (purulent drainage, necrosis).
- Positive intraoperative frozen section.

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and negative likelihood ratio of 8.45 and 0.15, respectively, for diagnosis of infection. Synovial fluid IL-6 was also significantly elevated in cases classified as infected in cases with *C. acnes* culture growth and in cases with a positive intraoperative frozen section compared to those with no positive frozen sections. Synovial fluid IL-6 significantly positively correlated with the total number (and percentage) of positive cultures per case.

In a second study that investigated the role of synovial fluid IL-6 in the diagnosis of shoulder PJI, Frangiamore et al. [4] prospectively examined intraoperative levels of 9 synovial fluid cytokines (IL-6, granulocyte macrophage colony-stimulating factor (GM-CSF), IL-1β, IL-12, IL-2, IL-8, interferon (IFN)-γ, IL-10, tumor necrosis factor (TNF)-α) in 75 cases of revision shoulder arthroplasty; 28 cases categorized as infected and 47 as not infected based on perioperative criteria (Table 1). The most commonly cultured bacteria was *C. acnes* (67% of cases), with CNSS the second most frequently cultured bacteria (25% of cases). Synovial IL-6, GM-CSF, IFN-γ, IL-1β, IL-2, IL-8 and IL-10 were significantly elevated in cases classified as infected; while IL-6, IL-1β, IL-2, IL-8 and IL-10 were significantly elevated in cases with *C. acnes* culture growth. Levels of all cytokines except TNF-α were significantly higher in revision cases with at least one positive intraoperative frozen section compared to those with no positive frozen sections, and moderately and significantly positively correlated (r = 0.41-0.68) with the total number (and percentage) of positive cultures per case, including IL-6. Individually, IL-6, IL-1β, IL-8 and IL-10 showed the best combined sensitivity and specificity for predicting infection (Table 2) with synovial IL-6 found to have an AUC of 0.87 with a high sensitivity (82%) and high specificity (87%) and a positive and negative likelihood ratio of 6.4 and 0.20, respectively, using a cut-off level of 453.6 pg/mL based on ROC analysis.

While IL-6 performed well as an individual diagnostic marker, it also performed well in combination with other synovial cytokines. A statistical model consisting of IL-6, TNF-α and IL-2 was found to have the optimal predictive power and showed better diagnostic test characteristics than any synovial cytokine alone with an AUC, sensitivity, specificity, positive and negative predictive value (NPV, PPV), and positive and negative likelihood ratio (LR+, LR-) of 0.87, 0.80, 0.93, 0.87, 0.89, 12.0 and 0.21, respectively (Table 2). A nomogram of the statistical model was developed and used to predict likelihood of infection for a patient.

(b) Serum

Several meta-analyses [5,6] have been performed on serum IL-6 in the hip and knee PJI literature with good diagnostic test characteristics reported, including sensitivity and specificity ranging from 72-97% and 89-91%, respectively. However, these results have not been replicated in the shoulder, likely due to the indolent nature and lower virulence of the common infecting organisms in the shoulder such as *C. acnes* and CNSS.

Villacis et al. [7] prospectively examined serum IL-6 levels in 34 cases of revision shoulder arthroplasty. Infection was defined as at least one positive intraoperative culture of peri-implant tissue with 14 cases categorized as infected and 20 as not infected. The most commonly cultured bacteria was *C. acnes* (64% of cases) with CNSS as the second most frequently cultured bacteria (29% of cases). There was no significant difference in the serum IL-6 levels between patients with and without infection. Serum IL-6 was found to have a sensitivity, specificity, positive predictive value, negative predictive

TABLE 2. Synovial fluid cytokine diagnostic test characteristic for infection

Cytokine	AUC*	Optimal Cut-off* (pg/mL)	Sensitivity	Specificity	PPV	NPV	LR+	LR-
IL-6	0.87	453.6	0.82	0.87	0.79	0.89	6.4	0.20
GM-CSF	0.70	1.5	0.54	0.85	0.68	0.75	3.6	0.55
IFN-γ	0.69	4.9	0.60	0.80	0.62	0.78	3.0	0.50
IL-1β	0.80	3.6	0.71	0.87	0.77	0.84	5.6	0.33
IL-12	0.60	6.0	0.36	0.94	0.77	0.71	5.6	0.69
IL-2	0.70	1.6	0.54	0.87	0.71	0.76	4.2	0.53
IL-8	0.78	1502.4	0.71	0.79	0.67	0.82	3.4	0.36
IL-10	0.76	28.1	0.72	0.82	0.69	0.84	4.0	0.34
TNF-α	0.60	4.5	0.92	0.33	0.43	0.88	1.4	0.24
Combined†	0.87	0.4	0.80	0.93	0.87	0.89	12.0	0.21

+, positive; -, negative; AUC, area under the curve; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LR, likelihood ration; NPV, negative predictive value; PPV, positive predictive value; TNF, tumor necrosis factor.

* AUC and optimal cutoff were determined using receiver operating characteristics curves. Sensitivity, specificity, PPV, NPV, LR+, and LR were determined from the receiver operating chararteristic curve analysis.

† Represents the diagnostic test characteristics of the combined 3-cytokine (IL-6, TNF-α, IL-2) model found to have the optimal predictive power. Reprinted with permission [4].

TABLE 3. Criteria for infection categories

Category	Criteria
No infection	All negative cultures (tissue or aspirate) and no preoperative or intraoperative* findings of infection
Possible infection	Negative preoperative or intraoperative* finding *and* 1 positive intraoperative culture
Probably infection	>1 positive intraoperative culture *and* negative preoperative or intraoperative* findings *or* At least 1 positive preoperative or intraoperative finding *and* 1 positive culture
Definite infection	At least 1 positive preoperative or intraoperative* finding of infection *and* >1 positive intraoperative culture *or* 1 positive preoperative (aspirate) culture *and* 1 positive intraoperative culture

Note: Positive preoperative aspirate has its own category because it is more definitive than these findings.

*Preoperative or intraoperative findings of infection: preoperative clinical signs (swelling, sinus tract, redness, drainage); positive ESR or CRP; positive frozen section; intraoperative gross findings (e.g., pus, drainage, necrosis).

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value and accuracy of 0.14, 0.95, 0.67, 0.61 and 0.62, respectively, using a cut-off level of 10 pg/mL.

Subsequently, Grosso et al. [8] prospectively examined serum IL-6 levels in 69 cases of revision shoulder arthroplasty; 24 cases categorized as infected and 45 as not infected based on perioperative criteria (Table 3). The most commonly cultured bacteria was *C. acnes* (83% of cases) with CNSS the second most frequently cultured bacteria (16% of cases). Only 6 cases in the study had an elevated serum IL-6 level, 3 in the infected group and 3 in the not infected group. Serum IL-6 was found to have a sensitivity and specificity of 12% and 93%, respectively, using a cut-off level of 5 pg/mL.

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QUESTION 3: Is there a role for synovial fluid white blood cell (WBC) count and differential in the diagnosis of shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: There may be a role, but synovial fluid cell count and differential currently lacks diagnostic thresholds from shoulder-specific literature.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

WBC count and polymorphonuclear leukocyte (PMN) percentage in synovial fluid continue to be used as parameters in the diagnosis of PJI [1–10]. As an indirect marker, synovial fluid WBC count and differential has been used as a reliable tool for diagnosing PJI of the lower

extremity [3,8,11]. However, shoulder-specific data is limited. The shoulder presents a unique challenge in diagnosis due to frequent culture growth of low-virulent organisms [12–14].

To evaluate the existing literature for use of synovial WBC and differential in the diagnosis of shoulder PJI, a PubMed search was undertaken with the query: "(periprosthetic OR PJI) AND shoulder AND (white OR WBC) AND (synovial OR aspirate)." This search provided three articles for review of which one was pertinent [15].

In a multicenter analysis of *C. acnes* PJI cases (as defined by original Musculoskeletal Infection Society (MSIS) criteria [16]), Nodzo et al. described the characteristics of the host inflammatory response in 18 knees, 12 hips and 35 shoulders [15]. They identified a significantly lower mean value for synovial WBC count for the shoulder (750 cells/ mm^3) compared to the knee (19,950 cells/ mm^3). This was, however, similar to the average reported for the infected hips (500 cells/ mm^3). Interestingly, the neutrophil percentage was similar between shoulders (90%) and knees (92.5%), while significantly lower for hips (61.0%). Unfortunately, while providing some insight into the inflammatory response to a low-virulent pathogen, this limited dataset was unable to calculate a diagnostic threshold or calculate sensitivity and specificity of synovial WBC for diagnosing PJI. As this analysis demonstrates a response commiserate with low-virulent infections of the hip, the diagnostic values reported for hip PJI (3,000 cells / mm^3 and 80% PMN) [3] may be the best current alternative.

WBC count and PMN percentage can remain high up to three months after arthroplasty. This limits the test utility in the first six postoperative weeks as a modified threshold has not been identified for the shoulder [17,18].

Compounding the uncertainty about the WBC count and PMN percentages as metrics that indicate shoulder PJI is the fact that shoulder synovial fluid aspirations frequently yield little to no fluid, a high percentage of "dry taps" [19,20].

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QUESTION 4: Is there a role for synovial cytokines in the diagnosis of shoulder periprosthetic (PJI)?

RECOMMENDATION: While not yet widely available, evaluation of cytokine levels in synovial fluid shows promise in clarifying the probability of shoulder PJI. See Questions 2 and 5 (Section 1.2. Prevention: Intraoperative) for discussion of specific cytokine evaluations.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Although the majority of previous literature on the use of cytokines for PJI diagnosis was focused on hip and knee arthroplasty [1–4], there are a number of recent publications regarding shoulder PJI [5–13]. It is established that shoulder PJI is often caused by less viru-

lent organisms than those in the hip or knee [5,7,12,14] with the most common microorganisms being- *Cutibacterium acnes* and coagulase negative Staph. Therefore, even though shoulder PJI might share some common characteristics to hip and knee PJI, a direct comparison is not suitable and more research specific to shoulder PJI is needed to establish concrete guidelines for the role of cytokines in these diagnoses [2,8,12].

Literature regarding cytokines (including interleukins IL-2, IL-4, IL-6, IL-8, IL-10) shows consensus that IL-6 is the most relevant cytokine biomarker for predicting shoulder PJI. Evidence supports that IL-6 has a sensitivity and specificity of approximately 90% and 95% respectively, as well as improved diagnostic accuracy when combined with IL-8 and IL-10 [7,9,11,15]. However, there remains some controversy regarding the use of IL-6 to determine resolution of infection after antibiotic and surgical treatment of PJI [16,17]. Applying this to current Musculoskeletal Infection Society criteria, IL-6 may be a useful adjunct however for diagnosis of resolution of infection although determination of resolution of infection still requires negative cultures and return of C-reactive protein and erythrocyte sedimentation rate to normal levels [11]. Cytokines were found to have the highest correlations with positive frozen sections [7], suggesting that the combination of cytokines and frozen sections may be a possible avenue for recommendations. The use of lateral flow immunoassay technique (QuickLine IL-6 Test) for IL-6 during surgery allows for rapid assessment of synovial fluid (17), but while it provides an acceptable specificity (97.6%), it has a weaker sensitivity (46.9%) [6].

Several published reports [7,9] describe cytokines as a strong predictor for shoulder PJI: one study with level 2 evidence [9], two level 3 [7,16], one level 4 [18], and one of level 5 [17]. The cutoffs for what constitutes a positive test are not well established and based on the frequently minimal inflammatory response to shoulder PJI, as suggested by Frangiamore et al., cytokine values for the diagnosis of shoulder PJI will likely be lower than those established for hip or knee infections. It also must be considered that there are studies reporting no infection with a cutoff under 10,000 pq; making imperative the need for other diagnostic tools for the assessment of shoulder PJI.

Although synovial fluid cytokines show promise as a preoperative or intraoperative tool to diagnose shoulder PJI, further validation is needed in the setting of shoulder PJI specifically, appropriate cutoff values must be further defined, and the tests must become rapid, affordable and widely available in order to truly impact clinical care.

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QUESTION 5: Is there a role for synovial fluid tumor necrosis factor-alpha (TNF-α) and interleukin (IL)-2 in the diagnosis of shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: There is a potential role for synovial fluid TNF-α and IL-2 in the diagnosis of shoulder PJI when interpreted in combination with other synovial fluid markers. TNF-α and IL-2 may not be as useful individually.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 0%, Abstain: 4% (Unanimous, Strongest Consensus)

RATIONALE

Several meta-analyses have been performed on synovial biomarkers in the hip and knee PJI literature, but with limited reports specifically on IL-2 and TNF-α [1,2]. In the only published article in the literature investigating the role for synovial fluid TNF-α and IL-2 in the diagnosis of shoulder PJI, Frangiamore et al. [3] prospectively examined intraoperative levels of 9 synovial fluid cytokines (IL-6, GM-CSF, IL-1β, IL-12, IL-2, IL-8, IFN-γ, IL-10, TNF-α) in 75 cases of revision shoulder arthroplasty; 28 cases categorized as infected and 47 as not infected based on perioperative criteria (Table 1). The most commonly cultured bacteria was *C. acnes* (67% of cases), with coagulase-negative Staphylococcus spp (CNSS) as the second most frequently cultured bacteria (25% of cases). Synovial IL-6, GM-CSF, IFN-γ, IL-1β, IL-2, IL-8 and IL-10 were significantly elevated in cases classified as infected; while IL-6, IL-1β, IL-2, IL-8 and IL-10 were significantly elevated in cases with *C. acnes* culture growth. Levels of all cytokines, except TNF-α, were significantly higher in revision cases, with at least one positive

TABLE 1. Periprosthetic shoulder infection criteria

Category	Criteria
Definite Infection	At least 1 positive preoperative or intraoperative finding of infection* and more than 1 positive culture (preoperative or intraoperative) *or* One positive preoperative culture (aspirate) and 1 positive intraoperative culture with the same organism
Probable Infection	At least 1 positive preoperative or intraoperative finding of infection* and one positive culture (preoperative or intraoperative *or* No preoperative or intraoperative findings of infection* and more than one positive culture (preoperative or intraoperative)
Probably Contaminant	No preoperative or intraoperative findings of infection* and one positive culture (preoperative or intraoperative)
No Evidence for Infection	No preoperative or intraoperative findings of infection* and no positive cultures (preoperative or intraoperative)

*Preoperative or intraoperative findings of infection:

- Preoperative clinical signs (swelling, sinus tract, redness, drainage).
- Positive result on serum erythrocyte sedimentation rate or C-reactive protein analysis. Intraoperative gross findings (purulent drainage, necrosis).
- Positive intraoperative frozen section.

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intraoperative frozen section compared to those with no positive frozen sections, and moderately and significantly positively correlated (r = 0.41-0.68) with the total number (and percentage) of positive cultures per case. Individually, IL-6, IL-1β, IL-8 and IL-10 showed the best combined sensitivity and specificity for predicting infection (Table 2). TNF-α was found to have an area under the curve (AUC) of 0.60 with a high sensitivity (92%) and low specificity (33%), while IL-2 was found to have an AUC of 0.70 with a low sensitivity (54%) and high specificity (87%).

While TNF-α and IL-2 did not perform as well as some of the other markers when assessed individually, combinations of synovial cytokines were also assessed for diagnostic performance using logistic regression analysis. A statistical model consisting of IL-6, TNF-α and IL-2 was found to have the optimal predictive power and showed better diagnostic test characteristics than any synovial cytokine alone with an AUC, sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratio of 0.87, 0.80, 0.93, 0.87, 0.89, 12.0 and 0.21, respectively (Table 2). A nomogram of the statistical model was developed and used to predict likelihood of infection for a patient.

While testing synovial fluid cytokine levels intraoperatively hold promise, these assays are not widely available at the present time and further study is needed.

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TABLE 2. Synovial fluid cytokine diagnostic test characteristic for infection

Cytokine	AUC*	Optimal Cut-off* (pg/mL)	Sensitivity	Specificity	PPV	NPV	LR+	LR-
IL-6	0.87	453.6	0.82	0.87	0.79	0.89	6.4	0.20
GM-CSF	0.70	1.5	0.54	0.85	0.68	0.75	3.6	0.55
IFN-γ	0.69	4.9	0.60	0.80	0.62	0.78	3.0	0.50
IL-1β	0.80	3.6	0.71	0.87	0.77	0.84	5.6	0.33
IL-12	0.60	6.0	0.36	0.94	0.77	0.71	5.6	0.69
IL-2	0.70	1.6	0.54	0.87	0.71	0.76	4.2	0.53
IL-8	0.78	1502.4	0.71	0.79	0.67	0.82	3.4	0.36
IL-10	0.76	28.1	0.72	0.82	0.69	0.84	4.0	0.34
TNF-α	0.60	4.5	0.92	0.33	0.43	0.88	1.4	0.24
Combined†	0.87	0.4	0.80	0.93	0.87	0.89	12.0	0.21

+, positive; -, negative; AUC, area under the curve; GM-CSF, granulocyte macrophage colony-stimulating factor; IFN, interferon; IL, interleukin; LR, likelihood ration; NPV, negative predictive value; PPV, positive predictive value; TNF, tumor necrosis factor.

* AUC and optimal cutoff were determined using receiver operating characteristics curves. Sensitivity, specificity, PPV, NPV, LR+, and LR were determined from the receiver operating chararteristic curve analysis.

† Represents the diagnostic test characteristics of the combined 3-cytokine (IL-6, TNF-α, IL-2) model found to have the optimal predictive power.

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QUESTION 6: Is there a role for synovial fluid leukocyte esterase strip testing in the diagnosis of shoulder periprosthetic joint injection (PJI)?

RECOMMENDATION: Given the current evidence, there is no role for synovial fluid leukocyte esterase (LE) strip testing in the diagnosis of shoulder PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Several meta-analyses [1–5] have been performed on synovial biomarkers in the hip and knee PJI literature, with multiple markers showing very good diagnostic test characteristics, including synovial LE strip testing. Lee et al. [1] found that the sensitivity, specificity, diagnostic odds ratio (DOR) and area under the curve (AUC) for synovial LE strip testing was 0.77, 0.95, 4.57 and 0.92, respectively, in one of these recent meta-analyses. Wyatt et al. [4] found that the sensitivity, specificity and AUC for synovial LE strip testing was 0.81, 0.97, and 0.97, respectively, in another of these recent meta-analyses. However, these results have not been replicated in the shoulder, likely due to the indolent nature of the common infecting organisms in the shoulder, *Cutibacterium acnes* (*C. acnes*) and coagulase-negative *Staphylococcus* species (CNSS).

In the only published article in the literature investigating the role for synovial fluid LE strip testing in the diagnosis of shoulder PJI, Nelson et al. [5] prospectively performed leukocyte esterase strip testing in 45 cases of primary shoulder arthroplasty and 40 cases of revision shoulder arthroplasty. Diagnosis of PJI was made based on Musculoskeletal Infection Society criteria. Ten patients (all revisions) met criteria for true PJI (n = 7) or potential PJI (n = 3). The sensitivity of LE strip testing, when including all of these patients as meeting the diagnosis of PJI, was only 30% and the specificity was only 67%. Positive predictive value was 43% and negative predictive value was 83%. When looking just at the presence of positive cultures, LE strip testing still had only a sensitivity of 25% and specificity of 75% for predicting a positive culture in the revision cases. In addition, a significant proportion of samples in the study were considered indeterminate (13.3% of primary samples and 22.5% of revision samples) because the aspirate was too bloody to interpret even after centrifugation. The authors concluded from this study that LE strip testing is an unreliable diagnostic test in shoulder PJI and should not be routinely used in the shoulder.

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QUESTION 7: Is there a role for synovial fluid alpha-defensin in the diagnosis of shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: Synovial alpha-defensin may aid in the diagnosis of shoulder PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Alpha-defensin is an antimicrobial peptide that is released by neutrophils in response to bacterial or fungal pathogens. The presence of alpha-defensin in synovial fluid has been thoroughly investigated as a biomarker for PJI following hip and knee arthroplasty with a reported 98% sensitivity and 100% specificity [1–11]. However, there is limited evidence regarding the use of alpha defensin as a biomarker for infection in shoulder arthroplasty.

Thirteen studies in the past three years have demonstrated the efficacy of this test in the diagnosis of hip and knee PJI, and better prognostic results have been reported compared to leukocyte esterase [3,6,9,11–14]. However, the role of alpha-defensin in diagnosing shoulder PJI is less well known. The literature contains only one study that specifically evaluated alpha defensin in shoulder arthroplasty. In this study by Frangiamore et al, alpha-defensin levels were obtained in 33 patients at the time of revision shoulder arthroplasty [6]. Patients were classified as infected or not infected by a standard criteria based on clinical evaluation, laboratory studies, histology and culture results. The area under the curve, sensitivity, specificity and positive and negative likelihood ratios for alpha-defensin in the diagnosis of infection were 0.78, 63%, 95%, 12.1 and 0.38, respectively. There was a significant difference in the median alpha-defensin level between the infection and no infection groups (3.2 [.21-4.74] versus .21 [.19-.23] p = .006). The authors concluded that alpha-defensin may be an appropriate test in the evaluation of infection in the painful shoulder arthroplasty.

A point of care device is now available for direct assessment of alpha-defensin in synovial fluid during surgical procedures (lateral flow immunoassay) [9,13]. Initial reports with this device report a 92% sensitivity and 100% specificity for the diagnosis of PJI in hip and knee arthroplasty [16]. However, some studies have concluded that the point of care lateral flow assay has a lower sensitivity and specificity when compared with the laboratory-based alpha-defensin test (sensitivity 77%, specificity 91%) [9,13,15]. This device has not been evaluated for the diagnosis of shoulder PJI.

Although the clinical presentation and diagnostic challenges are different in shoulder PJI than in hip and knee PJI, detection of high levels of alpha-defensin in synovial fluid in the shoulder could be a good predictor of infection. However, the cut-off values are not well defined, with authors reporting a range from 5.20-7.72 mg/L [16–18]. Further research and validation of alpha-defensin as a marker for PJI in shoulders is required.

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Author: Anders Ekelund

QUESTION 8: Is there a role for serum D-dimer in the evaluation of periprosthetic joint injection (PJI) following shoulder arthroplasty?

RECOMMENDATION: Unknown. There is currently only limited evidence related to the evaluation of hip and knee PJI and no study to date evaluating its use in shoulder PJI.

LEVEL OF EVIDENCE: No Evidence

DELEGATE VOTE: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A literature review (Medline, PubMed) was performed to identify relevant studies on the role for serum D-dimer in shoulder arthroplasty infections. Terms used included "periprosthetic infection," shoulder infection," "D-dimer," "diagnosing PJI," "serum biomarkers PJI." D-dimer is a fibrin degradation product, a small protein present in the blood after a blood clot is degraded. The D-dimer test has been used for diagnosing thrombosis, pulmonary embolus and disseminated intravascular coagulation (DIC). Lippi et al. [1] found that in an urban population the most common reason for an elevated D-dimer was infection (15%).

There has been a growing interest in the use of serum biomarkers to diagnose periprosthetic joint infections, especially given the imperfect nature of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) tests. A literature search found no studies regarding D-dimer and shoulder arthroplasty. There are however, reports in the hip and knee arthroplasty literature. Lee et al. [2] studied the postoperative levels of D-dimer after elective total hip arthroplasty. Only one paper was found regarding D-dimer as a diagnostic test for periprosthetic infection. Shahi et al. [3] reported on a prospective study of 245 patients undergoing primary arthroplasty (23), revision for aseptic failure (86), revision of PJI (57), reimplantation (29) and infection in a site other than a joint (50) (urinary tract infection, pneumonia, upper respiratory infection). The study included only hip and knee arthroplasties. The median serum D-dimer was significantly higher for patients with PJI and the 850 ng/mL was determined as the optimal threshold value for serum D-dimer for the diagnosis of a PJI. The sensitivity (89%) and specificity (93%) for serum D-dimer was better than for ESR, CRP and ESR & CRP combined. An interesting finding was that D-dimer was elevated in cases of *C. acnes* infection, a common pathogen in the shoulder which typically does not cause elevation in serum ESR or CRP. The authors concluded that serum D-dimer is a promising marker for the diagnosis of PJI.

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Authors: Jonathon Levy; Samer S. Hasan

QUESTION 9: Is there a role for preoperative joint aspiration in the evaluation of a shoulder arthroplasty for periprosthetic joint infection (PJI)?

RECOMMENDATION: Glenohumeral joint aspiration has a role as part of the investigation for shoulder PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Synovial fluid obtained from joint aspiration in the evaluation for PJI can be analyzed to determine nucleated cell count, culture and sensitivity, and various inflammatory markers (interleukin (IL)-6, tumor necrosis factor-α, and alpha defensin). Aspiration for culture is commonly performed. Controversy remains regarding the role of preoperative aspiration in the diagnosis of shoulder PJI. While multiple Level III and IV studies report using preoperative aspiration to evaluate a suspected shoulder PJI, many studies discuss the challenges of obtaining an adequate sample [1–3] as well as a variable incidence of false negative cultures [4,5]. In addition, the unique bacteriology of shoulder PJI, with a preponderance of the non-planktonic organism *C. acnes*, impacts the utility of shoulder aspiration in some clinical settings. No large study has adequately explored the predictive value of preoperative joint aspiration for synovial fluid culture in the diagnosis of shoulder PJI. Thus, there is limited evidence to support routine preoperative aspiration during the workup of a suspected shoulder PJI.

Millett et al. [6] reported on a series of 10 patients presenting with chronic shoulder pain arising after shoulder surgery. In all cases, a preoperative aspiration was carried out, but, in many cases, the tap was dry even after saline lavage. Infection was subsequently determined by positive bacterial culture from a sub-deltoid specimen [6].

In a retrospective multicenter review of infected reverse shoulder arthroplasties, Jacquot et al. [7] reported that preoperative joint aspiration was carried out in 14/32 (44%) cases and was positive in 12/14 (85%). They advocated joint aspiration before any single stage revision shoulder arthroplasty to determine the infective organism and antibiotic sensitivity that would allow selection of an appropriate antibiotic to include in the polymethylmethacrylate cement. Klatte et al. [8] reported on a series of 35 patients undergoing single stage exchange arthroplasty for shoulder PJI. All of the patients had preoperative joint aspiration. Antibiotics were withheld for two weeks prior to joint aspiration. Culture samples were incubated for 14 days, and the results were used to guide the choice of antibiotic added to cement at time of single stage revision. They felt their high cure rate after single stage treatment of shoulder PJI was due, in part, to the isolation of the infective organisms from the preoperative joint aspiration and the ability to add the appropriate antibiotics to polymethyl methacrylate cement as well as initiate the antibiotic treatment.

Ince et al. [4] reported on a series of patients undergoing single stage revision shoulder arthroplasty for shoulder PJI. Preoperative aspiration was performed in all patients and antibiotics were withheld for one week prior to aspiration. The authors were able to identify the infecting organism in 13/16 (83%) of the cases. Intraoperative biopsy and culture was needed to identify the infecting organism in the other three cases. Cultures were routinely held for 14 days to improve sensitivity.

Dilisio et al. [9] in a retrospective study compared the culture results of preoperative joint aspiration prior to arthroscopy to the results of intraoperative arthroscopic tissue biopsy. Fourteen of nineteen cases undergoing joint aspiration underwent fluoroscopic guidance with contrast to confirm intra-articular placement of aspiration needle. Only 1 of 14 patients (7%) had positive cultures. In contrast, 9 of 19 arthroscopic tissue biopsy cultures were positive. The authors reported that the sensitivity, specificity, positive predictive value and negative predictive value for arthroscopic biopsy was uniformly 100%. In contrast, preoperative aspiration had a sensitivity of 17%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 58%. The authors concluded that arthroscopic biopsy is better than preoperative aspiration for identifying shoulder PJI.

Ghijselings et al. [10] reported on 17 patients with shoulder PJI. The authors noted that 15 patients had preoperative cultures, but only 6 patients had undergone joint aspiration. Given the lack of a consistent protocol regarding preoperative joint aspiration, the authors did not comment on any recommended indication for joint aspiration. Sabesan et al. [11] reported on a retrospective review of 27 patients treated with two-stage revision for shoulder PJI. The authors recommended preoperative aspiration, if there was a high suspicion for infection. Twelve of 17 patients underwent aspiration. Fluid was available in 10/12 (83%) patients, and 6 of these had positive cultures.

Other reports have commented on the low yield of preoperative joint aspiration because of the high incidence of dry taps and/or false negative results. Sperling et al. [12] reported that preoperative joint aspiration was possible for only 56% of patients and that *P. acnes* was identified in less than 30%. Codd et al. [13] reported that aspiration was positive in only 39% of shoulders and that cultures were positive in about 29%. Romanó et al. [14] and Coste et al. [15] also reported that the preoperative joint aspiration was diagnostic in only 34-50% of the cases. Strickland et al. [5] reported that joint aspiration for shoulder PJI yielded a 34% false negative rate.

Finally, two review articles merit mention. Hsu et al. [16] evaluated 14 studies that attempted to define shoulder PJI. Of these, 4 used preoperative aspiration to identify the infective organisms. Mook and Garrigues [17] published a review article opining that preoperative serologies, synovial fluid cultures and synovial leukocyte count lacked the necessary specificity and sensitivity for diagnosis of shoulder PJI, especially those caused by *C. acnes* and other slow growing organisms. The authors conceded that, "There are no rigorous large-scale investigations available that address the following questions: (1) When is it appropriate to diagnostically aspirate a prosthetic shoulder joint? (2) If the decision is made to aspirate the shoulder prior to, or during, revision arthroplasty, what values of the synovial fluid leukocyte count are predictive of infection?" The authors add that guidelines for interpreting the results of joint aspirate are borrowed from hip and knee and are largely left up to surgeon judgment.

Based on our evaluation of the shoulder arthroplasty literature and consideration of data on hip and knee arthroplasty, we believe that aspiration of the shoulder joint being investigated for PJI may provide important information and should be attempted, when possible. We realize that a substantial number of these joint aspirations are likely to be dry or yield inadequate synovial fluid to allow all analyses. We also realize that shoulder joint aspiration can be performed with minimal risk and could provide critical information regarding the infective organism(s) and allow determination of the antibiotic sensitivity prior to surgical intervention.

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2.5. DIAGNOSIS: SAMPLING

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QUESTION 1: Should tissue samples be obtained for culture in all revision shoulder arthroplasties?

RECOMMENDATION: Tissue samples should be obtained for culture in all revision shoulder arthroplasties when there is suspicion for infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Prosthetic ioint infection (PJI) is a devastating complication following shoulder arthroplasty and varies between 0-5% with increasing risk in revision arthroplasty [1,2]. As such, organism identification and appropriate antibiotic administration is essential.

The failure to address infection without the relevant antimicrobial therapy results in poor outcomes with Coste et al. [3], reporting 30% residual infection when infected shoulder arthroplasty was treated with resection arthroplasty alone and 60% residual infection when purely antibiotic treatment was advocated. The appropriate surgical procedure, combined with the relevant antibiotic therapy, is therefore integral to the effective management of revision shoulder arthroplasty.

Aseptic loosening can be indistinguishable from acute infection and unexpected positive cultures are not uncommon and can be as high as 29% [4,5]. This is particularly relevant when considering the indolent nature of *Cutibacterium acnes*, a common shoulder pathogen, which can be isolated in as high as 60% of revision shoulder arthroplasties in which there were no positive preoperative or intraoperative investigations suggesting infection [5]. Tissue samples for culture should therefore be undertaken at the time of the procedure to both diagnose and confirm infection. Indeed, even in the presence of known infection, alternative organisms can be reported at the time of revision, which can also influence postoperative antibiotic therapy.

Interpreting positive cultures in a previously regarded aseptic revision can, however, be difficult due to false positives from contaminates. False negative results can also prove a challenge, particularly with regard to *Cutibacterium*, which can take 8-10 days to grow [6]. Extended culture incubation for a minimum of 10-14 days is, therefore, recommended [6,7]. Notwithstanding this, the multifocal and low-grade nature of chronic infection can lead to false negative cultures, and sampling bias must, therefore, be considered as a cause for negative cultures.

Mathematical modelling techniques have been utilised to mitigate the risk of false negatives, and it has been proposed that, following five or six specimens in predominantly revision hip and knee arthroplasty, infection can be diagnosed in the presence of three or more positive cultures [8]. In shoulder specific publications a minimum of four specimens have been advocated [9]. Furthermore, aseptic sampling techniques are imperative to minimize the risks of false positives [7,8,10].

Despite this, however, the staged treatment of infected shoulder arthroplasty can still result in residual infection with persistent infection reported in up to 22% of two-stage revisions which had completed implant explantation, debridement, antibiotic spacer and intravenous antibiotics for six weeks [11]. Tissue sampling and culture at the second stage of a two-stage revision shoulder arthroplasty is, therefore, still recommended to ensure optimal outcomes.

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QUESTION 2: Is there a role for obtaining tissue cultures when performing an irrigation and debridement (I&D) for hematoma after shoulder (primary or revision) arthroplasty?

RECOMMENDATION: Deep tissue samples should be routinely obtained and sent for culture when performing an I&D for hematoma after shoulder (primary or revision) arthroplasty.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 64%, Disagree: 28%, Abstain: 8% (Super Majority, Weak Consensus)

RATIONALE

A literature search of PubMed and Medline using the terms "shoulder" and "hematoma" resulted in 337 citations. After review of the abstracts, 11 articles that pertained to the topic of hematoma after shoulder arthroplasty were identified for full review. Due to the limited literature on hematoma and shoulder arthroplasty, references on the management of hematoma after total hip and knee arthroplasty were used in the development of this recommendation.

Postoperative hematoma is a known risk factor for prosthetic joint infection following hip and knee arthroplasty [1–3]. Although the supporting literature is scant, hematoma is often cited as a risk factor for the development of deep infection following shoulder arthroplasty as well [4–9]. A study by Cheung et al. retrospectively reviewed 3,541 primary and 606 revision shoulder arthroplasties and found that hematoma formation following shoulder arthroplasty was often accompanied by positive intraoperative cultures [9]. However, only 12 patients (30%) required hematoma evacuation. Nine of these patients had intraoperative cultures sent, and the cultures were positive in six patients. Two of the 12 patients ultimately required resection arthroplasty for deep infection.

In a case-control study Nagaya et al. found that patients with local hematoma formation after total shoulder arthroplasty and hemiarthroplasty had an increased risk for prosthetic joint infection (odds ratio (OR) = 7.10, 95% confidence interval (CI) 1.09-46.09, p = .04) on univariate analysis [10]. This association was lost in the multivariate analysis likely secondary to the low reported infection rate, although a trend towards significance persisted (OR = 6.51. 95% CI .84-50.70, p = .074).

While multiple other studies examining risk factors for the development of prosthetic joint infection following shoulder arthroplasty have been published, most do not specifically address the issue of hematoma formation. Some studies simply did not systemically collect data pertaining to hematoma formation [11–13] or, if they did, did not explore the statistical relationship between hematoma formation and subsequent prosthetic joint infection [8,14–19]. A few studies combined hematoma formation with other complications (e.g., wound dehiscence, superficial infection) when determining statistical associations with infection, making it difficult to determine the specific impact of hematoma formation alone [20,21].

Werner et al. reported on 58 consecutive patients undergoing reverse total shoulder arthroplasty and found that of the 12 patients (20%) requiring treatment for postoperative hematoma none developed any further complications requiring revision [22]. The rate of hematoma formation in the latter study, however, appeared to be very high compared to other reports, which may limit the generaliz-

ability of their results. In comparison, a prospective registry of 301 patients undergoing reverse total shoulder arthroplasty reported only one patient developing hematoma (0.33%) [23]. A systematic review of the literature, comprising 19,262 shoulder arthroplasty cases, found hematoma developed in only 0.51% of revision shoulder arthroplasty cases and 0.09% of total shoulder arthroplasty cases [24].

The presence of infection can be difficult to exclude based on gross findings at the time of hematoma evacuation. Based on the experience reported with arthroplasty of the hip and knee and the small amount of available literature specific to shoulder arthroplasty, we recommend that deep tissue samples be sent for culture routinely when performing an I&D for hematoma after shoulder arthroplasty. The data obtained from these culture samples are useful and can aid the treating orthopaedic surgeons in consultation with infectious disease specialists to determine the optimal management of these patients.

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QUESTION 3: Should tissue cultures be obtained in primary shoulder arthroplasty (SA) cases with history of prior surgery (arthroscopic, open, open reduction and internal fixation (ORIF), or another non-arthroplasty surgery)?

RECOMMENDATION: Obtaining tissue samples for culture in patients with history of prior non-arthroplasty surgery may be indicated in select cases.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Primary SA in patients with history of prior surgery in the affected shoulder is common. The reported prevalence is between 18%-23% [1,2], being higher in primary reverse shoulder arthroplasty (32% to 48%) [1,2] than in primary anatomic arthroplasty (11% to 14%) [1,2].

There is evidence demonstrating that prior surgery on a shoulder undergoing primary SA significantly increases the risk that a periprosthetic joint infection (PJI) will develop. Florschütz et al. [1] found that shoulders with prior surgery undergoing primary

SA demonstrated a significantly higher (p = 0.016) infection rate (4.3%) compared with shoulders with no prior surgery (1.3%), exhibiting a 3.35-times higher risk (95% confidence interval (CI), 1.28-8.81) for infection development. Werthel et al. [2] confirmed this finding in a cohort of 4,577 patients treated with primary SA. Of the 813, patients who had undergone prior surgery, 20 (2.46%) developed PJI. In contrast, of the 3,764 patients who did not have prior shoulder surgery only 48 patients (1.28%) developed PJI. This difference was significant in both the univariate (hazard ratio (HR), 2.08; 95% CI, 1.27-3.45; p = .0094 p = .0094) and multivariate analyses (HR, 1.81; 95% CI, 1.03-3.05 p = .0390). Additionally, a higher number of previous surgeries (HR, 1.68 per surgery) and SA for traumatic etiology (HR 4.49) were also significantly associated with an increased risk of PJI.

The mechanism by which prior surgery increases the risk of PJI is unknown. Possibilities include deep tissues open to the environment with increased operative time both during the index surgery and the arthroplasty [3]; altering the ability to combat infection by affecting lymphatic drainage and blood supply of periarticular tissues [3]; or perhaps, organisms, such as *Cutibacterium Acnes,* may colonize the shoulder and the hardware at the time of the index surgery and remain quiescent or as a low-grade infection until an arthroplasty is performed, which provides a larger surface area of prosthetic material for establishment of a biofilm [2]. There is evidence of subclinical low-grade infections without overt signs of infection by *C. acnes* after arthroscopic and open non-arthroplasty surgery [4–7]. Therefore, while we can make no definitive recommendation given the lack of data in patients undergoing SA subsequent to prior non-arthroplasty surgery, it is reasonable to consider sending intraoperative tissue samples for culture to screen for possible low-grade subclinical infections or wound contaminations.

A comprehensive review of the literature on cultures from tissue samples in primary arthroplasty with history of prior surgery was performed and did not find any prospective or randomized studies. While there is lack of evidence for positive cultures in patients with history of prior surgery, there are a number of studies that investigate patients undergoing primary arthroplasty without prior surgery. Levy et al. [8] isolated *C. acnes* from the synovial fluid and tissue prior to prophylactic antibiotics in 41.5% of shoulders undergoing shoulder replacement for osteoarthritis. In this study, *C. acnes* infection was defined as a positive culture in 50% or more of specimens collected (swab or tissue). Maccioni et al. [9] reported positive tissue cultures for *C. acnes* in 3.1% of cases . Matsen et al. [10] collected 50 tissue samples from 10 patients undergoing primary SA without a history of prior surgery after aggressive prophylactic antibiotic and skin preparation and reported that 14% were positive for *C. acnes*. Falconer et al. [11] evaluated the contamination of the surgical field by *C. acnes* in patients undergoing primary SA without history of prior surgery. The rate of one or more positive swab cultures was 33%. The most common site of growth of *C. acnes* was the subdermal layer. Koh et al. [12] assessed the rate of *C. acnes* colonization in patients undergoing primary shoulder arthroplasty. Patients with prior surgery were excluded. Thirteen patients (43%) had positive deep swab cultures on entering the glenohumeral joint. While in these studies there is variability of the reported rates that might reflect the heterogeneity in the culture techniques and the different definitions used to define a positive culture, there is a consistent finding of positive cultures in primary arthroplasties without a history of prior surgery. The clinical relevance of positive cultures from shoulder undergoing primary surgery is unclear.

In light of reports of positive tissue cultures from shoulders without prior surgery, the utility of intraoperative tissue cultures in patients undergoing primary SA with a history of prior surgery is unclear. Further research into the results of cultures in primary arthroplasty with history of prior surgery using standardized culture techniques and better methods to interpret the results is warranted.

Given the lack of evidence, the use of intraoperative tissue samples for cultures in patients undergoing primary SA with history of prior surgery as a screening infection test should be used at the discretion of the treating surgeon. No universal recommendation can be made at this time. However, considering that low-grade infections actually occur after arthroscopic and open shoulder surgeries and that prior surgery is a demonstrated risk factor for PJI, a screening strategy involving a selected group of patients based on the presence of risk factors (multiple prior surgeries; prior failed ORIF; male gender; younger patients may be prudent [1,2,13,14].

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QUESTION 4: Is there a role for preoperative open or arthroscopic tissue biopsy in the evaluation prior to initial revision shoulder arthroplasty?

RECOMMENDATION: Arthroscopic or open biopsy prior to initial revision shoulder arthroplasty can aid in the diagnosis of suspected shoulder periprosthetic joint infection (PJI).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

PubMed and Embase were searched from 1980 to January 2018 to identify studies evaluating preoperative open or arthroscopic tissue biopsy prior to revision shoulder arthroplasty. A secondary search of the references of included studies was also conducted. Three articles were selected for inclusion. Articles regarding hip and knee arthroplasty were excluded.

Morman et al. described one case in which arthroscopy was used in the evaluation of shoulder PJI prior to revision [1]. The patient presented with pain and glenoid loosening three years after total shoulder arthroplasty (TSA), underwent arthroscopic tissue biopsy that grew *C. acnes*, and went on to undergo successful two-stage revision for shoulder PJI.

Dilisio et al. reported on a series of 19 cases from a series of 350 painful shoulder arthroplasties who underwent arthroscopic biopsy prior to revision [2]. At revision shoulder arthroplasty, 41% had positive cultures, all for *C. acnes*. Arthroscopic biopsy prior to revision was exactly consistent with the final revision cultures with 100% sensitivity, specificity, positive predictive value and negative predictive value. The authors also reported that fluoroscopically guided glenohumeral aspiration prior to revision was inferior to arthroscopic biopsy with 16.7% sensitivity, 100% specificity, 100% positive predictive value and 58.3% negative predictive value. There are potential limitations including selection bias in this study without well-defined criteria by which the 19 patients out of 350 painful TSAs were selected to undergo arthroscopy. Thus, it is unclear what features of the presentation led the treating surgeon to continue to have a high index of suspicion for infection in these particular cases. Furthermore, cultures were held following revision surgery for only 7 days, whereas many authors advocate for longer incubation times (most frequently 14 days) for the fastidious and slow-growing *C. acnes*.

Tashjian et al. reported on a series of 77 patients who had revision TSA, and pre-revision biopsy was performed in 17 cases considered "at-risk" for infection [3]. Specifically, this included patients with abnormal erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) with no growth on shoulder aspiration, as well as patients with normal ESR/CRP and a dry aspirate. Patients that were grossly infected, those with positive aspiration culture, as well as those with normal ESR/CRP and negative aspiration culture were not biopsied. Open biopsy was performed for cases of known deficient rotator cuff via the proximal 3cm of the prior deltopectoral incision. Arthroscopic biopsy was performed with anatomic TSA with intact rotator cuff via a posterior viewing portal and anterior rotator interval portal for obtaining biopsy specimens. Two to three samples were obtained during biopsy and again at the time of revision TSA, and cultures were held for 14 days. Revision arthroplasty was performed at least three weeks after biopsy. They found that the prerevision biopsy resulted in 75% sensitivity, 60% specificity, 82% positive predictive value and 50% negative predictive value for the prediction of positive culture at the time of revision TSA. For diagnosis of infection, sensitivity was 90%, specificity 85%, positive predictive value 90% and negative predictive value 86%. The study limitations include a mixture of open and arthroscopic biopsies prior to revision TSA, a small sample size, and the use of two biopsy samples in some patients and three in others. There was also no comparison between open and arthroscopic biopsy and no comparison to other diagnostic tests.

Overall, the limited available literature suggests that biopsy prior to revision TSA can improve the diagnosis of shoulder PJI in cases without obvious objective evidence of infection, where the clinician remains suspicious of occult infection. While not well studied, many clinicians have used this technique as a method to confirm an aseptic environment before implantation of a prosthetic in cases where there is a distant history of apparently fully treated infection after shoulder surgery. Future research must report which history, demographic, physical exam, radiographic or laboratory features can guide a clinician to continue to be suspicious of occult infection. There is no evidence for a role in cases that are obviously infected or cases without suspicion for infection (e.g., loosening after trauma or loosening after many years of successfully functioning shoulder arthroplasty where labs are normal and radiographs do not suggest infection). Specific indications for arthroscopic biopsy remain to be further defined due to the limited available literature at present. Perhaps the main advantage of pre-revision biopsy for culture is that if the cultures are positive one might make the definitive decision to perform two-stage revision and have a better understanding of appropriate antibiotic management. However, it also remains unclear if this would be the appropriate decision given the good track record of one-stage revision TSA in cases of unexpected positive cultures for *C. acnes*. In addition, the cost-effectiveness of adding an arthroscopic biopsy to the treatment algorithm for revision shoulder arthroplasty remains unknown.

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QUESTION 5: Does the sampling technique (number of samples, anatomic locations) of the tissue obtained in the evaluation for shoulder periprosthetic joint infection (PJI) affect the result of frozen section and permanent histology?

RECOMMENDATION: Obtaining samples from multiple locations—most importantly from the prosthetic interface membranes—may optimize accuracy if performing frozen section or permanent histology as part of a workup for periprosthetic shoulder infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 91%, Disagree: 0%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

Frozen section histology can be useful in the diagnosis of shoulder PJI [1]. Two studies have specifically assessed the use of frozen section in revision shoulder arthroplasty [1,2]. These analyses did not offer specific guidance on the tissue sampling technique for histologic analysis in the shoulder. Topolski et al. stated only that "a biopsy specimen from the synovial surface that appears most inflamed is usually sent for histologic evaluation of frozen sections" [2]. Alternatively, Grosso et al. suggested sampling deep periprosthetic tissue—specifically tissue obtained from the membranes of the glenoid or humeral components [1].

Due to the lack of evidence addressing the optimal sampling technique in shoulder-specific literature, a broad systematic review of all arthroplasty literature was undertaken. A search was performed on Scopus [3] with the query, "(joint OR hip OR knee OR shoulder) AND (arthroplasty OR replacement) AND (infection OR infected) AND ('frozen section' OR histology OR histologic)." This provided thirty-eight articles of interest to this topic. Twenty-five of these articles reported the number of samples obtained and/or their anatomic location—most of which described obtaining samples from multiple sites, including the prosthetic membrane interface and inflamed-appearing synovium. Two articles resulting from this query, however, provide specific analysis of intraoperative sampling technique for histologic analysis.

Wu et al. performed a review of lower-extremity revision arthroplasty cases with specific focus on histologic analysis using a non-standard definition of PJI (based upon purulence, culture-results and histologic analysis) as the gold-standard [4]. This analysis found increased sensitivity for frozen section when increasing the number of samples (76%, 86% and 86% for three, five, and seven samples, respectively) with decreasing specificity (97%, 96% and 92%). From this, the authors concluded that the most accurate use of frozen section is sampling of five sites with a single positive sample (using Feldman's adoption of Mirra's criteria [5,6]) deemed as diagnostic of PJI. Unfortunately, the authors did not clarify if this sub-analysis was performed as a simulation and how samples were excluded.

Bori et al. investigated the association between anatomic location of the tissue sample and the accuracy of frozen section analysis [7]. In their review of 69 revision hip arthroplasties, they found that frozen section of tissue taken from the prosthetic interface membrane compared to pseudocapsule had improved sensitivity (83% versus 42%) with identical specificity (98%). Unfortunately, these authors used a non-standard definition of PJI. They also excluded patients who were ultimately diagnosed with PJI based upon intraoperative testing and appearance but were presumed to have aseptic loosening preoperatively.

While limited, the two lower extremity arthroplasty studies suggest that the most accurate utilization of intraoperative frozen section is conferred by obtaining multiple frozen sections from the prosthetic interface membrane [4,7]. This is in concert with the single study finding benefit of frozen section in the setting of shoulder revision arthroplasty [1]. Further evidence is necessary to confirm this recommendation.

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QUESTION 6: Is there a role for sonication of retrieved shoulder implants in the diagnosis of shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: There is currently no evidence to support routine sonication of the retrieved shoulder implant in the diagnosis of shoulder PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

PubMed and Embase were searched from 1980 to January 2018 to identify studies evaluating the role of sonication of retrieved implants in shoulder PJI. A secondary search of the references of included studies was also conducted. Prior work has evaluated the role of sonication of retrieved implants in hip and knee arthroplasty. In some of these scenarios, sonication of implants has been used to improve PJI culture sensitivity via disruption of bacterial biofilms (see Hip and Knee, Section 2.4. Pathogen Isolation, Culture Related Matters, Question 6 for full discussion of available literature and recommendations from the International Consensus Meeting (ICM) on musculoskeletal infection) [1–7]. Our search identified two studies that have evaluated the role of implant sonication specifically in the setting of shoulder PJI [3,5].

Piper et al. compared periprosthetic tissue culture and implant sonication followed by sonicate fluid culture from 136 shoulder arthroplasty revisions performed for any indication between 2004 and 2008 [5]. For the sonicate fluid culture, a cutoff of > 20 colony forming units per milliliter was used to exclude contaminants. Thirty-three cases had a definite shoulder PJI and 2 had probable shoulder PJI. The sonicate fluid culture showed slightly better sensitivity for detecting shoulder PJI compared with periprosthetic tissue culture (66.7% vs. 54.5%, p = 0.046). There was no difference in specificity (98% vs. 95.1%, p = 0.26). The authors concluded that sonication improved the diagnosis of shoulder PJI.

Grosso et al. compared intraoperative tissue and fluid culture to sonication fluid culture for 53 revision total shoulder arthroplasty procedures, of which 25 were identified as shoulder PJI [3]. The sensitivity and specificity of the intraoperative cultures were 96% and 75%, respectively. Using a cutoff of > 20 colony forming units per milliliter, the sonication fluid culture had sensitivity and specificity of 56% and 93%, respectively. While the sensitivity was greater for intraoperative culture than sonication (p = 0.001), there was no difference in specificity (p = 0.07). The authors concluded that implant sonication had no benefit in comparison to standard intraoperative cultures for shoulder PJI diagnosis.

The Piper et al. and Grosso et al. studies differed in several ways including the diagnostic criteria for shoulder PJI (2 positive cultures vs. 1 positive culture with other signs of infection), length of culture (7 days vs. 12 to 14 days) and the sonication methods. Overall, the conflicting results of these two limited studies make it unclear whether sonication can improve diagnosis of shoulder PJI.

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QUESTION 7: Should preoperative antibiotics be held until after cultures are obtained in revision shoulder arthroplasty (RSA)?

RECOMMENDATION: Recent studies have shown that preoperative antibiotic prophylaxis does not adversely affect intraoperative culture results. We do not recommend routinely holding preoperative antibiotics in RSA.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

In a systematic review using the Cochrane Library, Medline, Embase and CINAHL (Cumulative Index to Nursing and Allied Health Literature) databases, it has been reported that intravenous antibiotic prophylaxis reduces the risk of absolute infection by 8% and the risk of relative infection by 81% in patients who underwent a primary or revision total hip replacement or total knee replacement [1]. On the other hand, it has been shown that the identification of pathogen and pathogen-specific antibiotic therapy are extremely important in the treatment of periprosthetic joint infection (PJI) [2,3]. In the Report of the Third International Consensus Meeting, withholding preoperative antibiotics was not routinely recommended for the operative treatment of the knee and hip PJI [4,5]. However, it has been stated that antibiotics might be held in cases where the pathogen is not identified preoperatively [4]. In contrast to bacteria with high antigenicity that cause suppurative infection and sepsis clinically, low virulence *C. acnes* (*Cutibacterium acnes*) is responsible for the majority of shoulder PJI [6,7]. The culture sensitivity is poor for this pathogen [6]. It may be helpful to utilize implant sonication [8], next-generation sequencing and polymerase chain reaction (PCR) technologies to increase the sensitivity of detecting this low-virulence bacterium [3]. However, those techniques are not used routinely in current clinical practice due to fact that they are not cost-effective and require additional equipment [9]. Given these difficulties, it is important to anticipate whether preoperative intravenous antibiotic prophylaxis will reduce culture sensitivity. Pottinger et al. [10] evaluated the effects of antibiotic prophylaxis on the culture positivity in patients who underwent RSA with a diagnosis of shoulder PJI (at least 2 cultures being positive). In the patient group for which antibiotics were held, the cultures were more than twice as likely to be positive for *C. acnes* and other organisms versus the group of patients where antibiotics had not been held. However, this is a retrospective study and the decision to hold antibiotics was dependent on the operating surgeon. There might be bias on holding antibiotics for a case that the operating surgeon thought might be infected rather than not. There is insufficient literature in this regard with limited evidence. In the majority of RSA studies, although the effect of antibiotic prophylaxis on culture positivity has not been directly examined, it has been observed that clinicians have a tendency to hold preoperative antibiotic prophylaxis in revision shoulder arthroplasty [10–13]. However, in the Clinical Practice Guideline issued by the Infectious Diseases Society of America, the importance of evaluating preop PJI risk was emphasized in the decision to hold antibiotic prophylaxis. If the history, examination, erythrocyte sedimentation rate, C-reactive protein level and preoperative aspiration suggest that the risk of PJI is low, preoperative antibiotic holding is not recommended. Preoperative antibiotic holding is only recommended in cases where the infection is strongly suspected [14].

A study directly examining the effect of preoperative antibiotics on culture results in RSA was performed recently by Anagnostopoulos et al. The authors assessed the influence of antibiotic prophylaxis within 30 to 60 minutes before surgery on time to positivity of intraoperative cultures and the proportion of positive intraoperative cultures [15]. One-hundred-ten patients who underwent revision shoulder, hip or knee arthroplasty were included in the study. Seventy-two patients underwent RSA and the culture of *C. acnes* was evaluated directly. Among the 64 patients with *C. acnes* infection, the proportion of culture positivity was 71.6% (95% confidence interval (CI) 64.1-79.1) in the patients without perioperative prophylaxis, whereas the proportion of culture positivity was 65.9% (95% CI 55.3-76.5) in the patients with perioperative prophylaxis. This was not a statistically significant difference ($p = 0.39$).

In a study by Matsen et al. [16], intraoperative positive cultures for *C. acnes* could be obtained even when using intravenous antibiotic prophylaxis in the setting of a primary shoulder replacement. Similar to Matsen et al., Phadnis et al. [17] reported obtaining positive culture for *C. acnes* from the shoulder dermis despite skin preparation and prophylactic antibiotics.

Based on the available limited literature, considering that the importance of protecting the newly implanted hardware and avoiding surgical field infection are of utmost importance, we recommend that preoperative antibiotics should not be held until after cultures are obtained in RSA.

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QUESTION 8: Does the sampling technique (e.g., number of samples, tissue versus fluid versus implant, anatomic locations) affect the results for culture of specimens obtained in the evaluation of shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: We recommend five deep tissue specimens for culture be obtained from various surgical sites (e.g., capsule, humeral canal and periprosthetic membranes in the proximal humerus and glenoid). Use of swabs is discouraged. Fresh instruments should be used to obtain and place samples directly into sterile containers. Fluid sampling may be beneficial but has lower yield compared to tissue.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The shoulder presents a unique challenge in evaluating and treating PJI. The diagnosis of PJI is currently heavily reliant on culture results around the time of revision surgery. These culture results are frequently positive—often unexpectedly [1–4]—and the implications have yet to be fully elucidated [5–8]. To understand the most effective methods for obtaining samples for culture, a systematic review of the existing literature was undertaken. A Scopus [9] search was performed with the query, "(shoulder OR "upper extremity") AND (arthroplasty OR replacement OR revision) AND (culture OR microbiologic OR microbiology)." The resulting titles and abstracts (n = 218) from this query were reviewed for any pertinence to the question of number of samples for culture, specimen type and anatomic locations. All pertinent articles (n = 28) were then fully reviewed, and any other pertinent citations in these gathered articles were obtained and reviewed.

In cases concerning for possible shoulder PJI an attempt to make a preoperative case for surgical planning is desirable. Historically, preoperative joint aspiration and fluid culture has served in this endeavor. However, recent evidence has demonstrated a poor sensitivity of fluid cultures [6,10–12]. Three separate analyses out of a single institution repeatedly demonstrated decreased rates of positive cultures (27-38%) from fluid specimens compared to solid tissue (34-66.5%) and explants (46-55.6%) [6,10,11]. In a separate analysis, Dilisio et al. compared arthroscopic biopsy results (a minimum of three samples) and preoperative fluroscopically-guided aspiration for culture in patients who went on to open revision arthroplasty [12]. They found that arthroscopic biopsy had 100% concordance with culture at the time of open surgery; however, aspirated fluid had a sensitivity 16.7% and specificity of 100%. However, while these data suggest that fluid aspiration is not the optimal specimen type for culture, it is less invasive compared to arthroscopic biopsy.

Another potential source for culture is sampling of the explanted components. In separate analyses, Lucas et al. and Ahsan et al.demonstrated similar positive culture results from explant vortex samples and solid tissue cultures [6,10]. Lucas et al. also found that 56% (24/43) of loose glenoid components were culture-positive after vortex sampling compared to 13% (1/8) of stable glenoid components [6]. However, in 53 patients undergoing revision shoulder arthroplasty (25 infections), Grosso et al. found that cultures of fluid from explant sonication had a sensitivity and specificity of 56% and 93%, respectively, when using a threshold of 20 colony-forming-units (CFU) per milliliter (mL) [13]. When removing this threshold, the sensitivity improved to 96% but the specificity decreased to 64%. This was compared to 96% and 75% sensitivity and specificity, respectively, for solid tissue cultures. Unfortunately, this analysis excluded those patients that received preoperative antibiotics—a population that has historically benefited the most from explant sonication cultures [14]. In a separate analysis of 136 revision or resection shoulder arthroplasties, Piper et al. was unable to find a statistically-significant improvement in sensitivity of explant sonication (66.7%) compared to solid tissue cultures (54.5%) [15]. Despite this, the authors advocated for explant sonication. However, taking into account all of the existing literature specific to shoulder PJI, there is little support for routine use of explant culturing in revision shoulder arthroplasty.

When collecting solid tissue for culture, a common question is the optimum location and number of samples. Specifically in the shoulder, Pottinger et al. and Frangiamore et al. demonstrated a positive correlation between the number of samples taken and the number of positive culture results [4,16]. Pottinger et al. found an odds ratio for positive culture results of 1.24-1.35 per sample obtained [4]. Frangiamore, however, found no association between the number of samples obtained and the proportion of samples that were positive [16]. In an analysis of *C. acnes* in revision shoulder arthroplasty, Matsen et al. determined that, given their proportion of positive cultures, four specimens would provide a 95% chance of detecting the organism [11]. With the goal of increasing the sensitivity of tissue culture without additional costs of unnecessary cultures and sacrificing specificity, the appropriate number of samples can be a difficult target, aggravated by the current lack of a uniform definition of PJI specific to shoulder arthroplasty [17]. From the general arthroplasty literature, Atkins et al. reviewed 297 revision hip and knee arthroplasty cases with modeling to determine that five to six specimens provided the best sensitivity and specificity of PJI diagnosis with a target of two positive cultures [18]. In a more recent analysis, Peel et al. reviewed 499 patients undergoing arthroplasty (60 shoulders) using the Musculoskeletal Infection Society (MSIS) definition of PJI [19,20]. Using the results of their review, they performed mathematical modeling to determine that the optimal number of samples for standard tissue culture was four. Unfortunately, the use of the modified MSIS definition of PJI may confound the results of their analysis as applied to shoulder arthroplasty—known to be a more indolent presentation of infection. Given this current evidence, it is recommended that four to five samples be obtained during revision shoulder arthroplasty to minimize cost and likelihood of false-positive results while increasing culture sensitivity in revision shoulder arthroplasty.

In determining the best locations for specimen selection, it is first imperative to sample from any sites consistent with active infection through signs of inflammation, acute purulence or necrosis. In their analysis of the origin of *C. acnes* positive cultures in revision shoulder arthroplasty, Matsen et al. found that periprosthetic

membranes, especially the humeral membrane, had the highest rate of positive cultures for *C. acnes* [11]. For arthroscopic evaluation of PJI, Dilisio et al. biopsied at least three different sites with evidence of synovitis and prosthetic contact [12].

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Treatment

3.1. TREATMENT: ANTIBIOTICS FOR UNEXPECTED POSITIVE CULTURES

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QUESTION 1: Is there a role for postoperative antibiotics after performing an irrigation and debridement (I&D) for hematoma complicating a primary or revision shoulder arthroplasty while awaiting culture results?

RECOMMENDATION: Antibiotics should be given after performing an I&D for hematoma after shoulder (primary or revision) arthroplasty while awaiting cultures.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 91%, Disagree: 9%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

A literature search using the terms "shoulder" and "hematoma" resulted in 337 in citations. After review of the abstracts, 11 articles [1–11] that pertained to the topic of hematoma after shoulder arthroplasty were identified for full text review. Review of these 11 articles did not identify any specific studies addressing the use of antibiotics after performing I&D of a hematoma after shoulder arthroplasty. However, given the concern for the presence of infection at the time of I&D for hematoma following shoulder arthroplasty, as discussed in Section 2:5, Question 2 ("Is there a role for obtaining wound cultures when performing an I&D for hematoma after shoulder (primary or revision) arthroplasty?"), we believe it is reasonable to initiate empiric antibiotic treatment while awaiting the culture results. In our clinical practice, oral antibiotics (frequently doxycycline) are used pending final culture results, though there is no clinical outcomes data to justify a particular antibiotic selection, route or even the use of antibiotics at all in this setting.

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QUESTION 2: Is there a role for postoperative antibiotic treatment for revision arthroplasty with subsequent unexpected positive cultures for a virulent organism (e.g., methicillin-resistant *S. aureus* (MRSA), methicillin-sensitive *Staphylococcus aureus* (MSSA) or E. coli)?

RECOMMENDATION: In aggregate, published studies do not clearly show superiority for prolonged antibiotic use over no prolonged antibiotic treatment in the setting of revision shoulder arthroplasty with subsequent cultures positive for virulent organisms. However, the data on this specific clinical scenario is limited as the vast majority of unexpected positive cultures are with less virulent organisms (e.g., *C. acnes*, Coagulase-negative *Staphylococcus* (CNS)).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive literature review was performed to identify all studies on prophylactic/suppressive antibiotics after revision shoulder arthroplasty. Searches for the terms "shoulder replacement," "infection," "antibiotics," "postoperative" and "joint replacement" were performed using the search engines PubMed, Google Scholar and Cochrane review, which were searched through February 2018. Inclusion criteria for our systematic review were all English studies (Level I-IV evidence) that reported on antibiotic prophylaxis, or lack thereof, in cases of revision shoulder arthroplasty. Exclusion criteria were non-English language articles, nonhuman studies, retracted papers, incomplete antibiotic records, case reports, review papers, studies without clinical follow-up/infection rates, and technique papers without patient data. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed.

The prevalence of subclinical infections (unexpected positive culture (UPC)) is common with shoulder arthroplasty due to anatomic and demographic factors. The rate of positive cultures in primary and revision arthroplasty settings have been reported as high as 56 % [1–3], although much lower for virulent organisms. However, the significance and optimal treatment for UPCs caused by virulent organisms remains unknown. There is limited data in the shoulder literature for or against any role for postoperative prophylactic/suppressive antibiotics after revision shoulder arthroplasty without clinical or radiographic signs of infection. While several studies described the use of prophylactic or suppressive antibiotics after revision shoulder arthroplasty, there were no prospective randomized studies and none of the studies specifically evaluated efficacy by antibiotic or organism type.

Among the published studies for outcomes after revision shoulder arthroplasty with subclinical presentations and unexpected positive cultures, all were retrospective studies with differing methodologies [4–8]. All of the studies reported the majority of positive cultures (> 80%) from indolent organisms (*C. acnes* and/or CNS). None of the studies found a detrimental effect to NOT prescribing prolonged antibiotics postoperative, although one study with no comparison group reported a 25% recurrence rate after UPC. In studies that treated UPC with prolonged antibiotics, recurrence rates were low (0-3.5%). One systematic review confirmed a pooled "true infection" rate after UPC of 10.2%, with antibiotic use not influencing the rate of occurrence of "true infection" after UPCs (P = 0.498) [9].

Grosso et al. used antibiotic cement and 24 hours routine postoperative antibiotics with 1 superficial infection and no deep infections after revision shoulder arthroplasty [4]. Foruria et al. reported at least a 10% persistent infection rate after single stage shoulder arthroplasty revision, although antibiotic use and positive cultures did not influence the rate of true infection. [5]. Padegimas et al. reported a 23.9% UPC rate after revision shoulder arthroplasty with standardized UPC treatment of 6 weeks antibiotics or 2 weeks antibiotics at surgeon discretion . They found only 1 recurrent infection in the UPC group, 3.5% versus 3.4% in the non-UPC group [6]. Kelly et al. reported 8/28 (29%) UPC rate after revision shoulder arthroplasty, and only treated one with antibiotics postoperatively for 4 weeks (due to superficial wound infection). Of 8 patients, 2 (25%) developed late clinical infection with *C. acnes* [8]. Lastly, Hsu et al. reported a 49% positive culture rate after revision shoulder arthroplasty, and treated patients based on a protocol of 6 weeks IV and 6 months of oral antibiotics if > 2 cultures positive. Zero percent of patients had recurrence of infection with this protocol in the positive culture group and negative culture groups [7]. On the other hand, risks from prolonged antibiotic use are significant. Two studies reported a 19-42% complication side-effect rate from its use, which was seen in both oral and intravenous medication use [4,7].

The vast majority (> 80%) of UPC's reported in the shoulder literature were *P. acnes* or CNS organisms. Due to small numbers, meaningful comparisons to more virulent organisms could not be performed. Other studies in the lower extremity literature suggest that periprosthetic joint infections from virulent organisms have higher reinfection rates despite surgery (45-49%) for MRSA, Enterococcus and Streptococcus [10–12]. In the lower extremity arthroplasty literature, there was one randomized controlled study which found a limited benefit associated with prolonged oral antibiotic therapy after two-stage revision with negative cultures (5% versus 19%), although culture profiles from the reinfections (mostly virulent) tended to differ from the original infection organism profile [13].

In aggregate, these studies do not clearly show superiority for prolonged antibiotic use over no prolonged antibiotic treatment in the setting of revision shoulder arthroplasty with subsequent cultures returning for virulent organisms. The clinical implications may differ between occult PJIs and unsuspected PJIs in that preoperative diagnostic tests may be performed in the occult PJI setting, which may guide future treatment pathways. Prolonged antibiotic therapy may not be necessary in those patients with low suspicion of infection. In addition, there are well-reported risks of antibiotic related side-effects and resistance with widespread use.

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QUESTION 3: Is there a role for postoperative antibiotic treatment when a revision arthroplasty is performed with subsequent unexpected positive cultures of the shoulder caused by an indolent organism (e.g., *C. acnes* or coagulase-negative *Staphylococcus*(CNS))?

RECOMMENDATION: Postoperative antibiotic treatment beyond 24 hours after revision arthroplasty with unexpected positive cultures for an indolent organism does not appear to reduce the risk of subsequent infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 84%, Disagree: 4%, Abstain: 12% (Super Majority, Strong Consensus)

RATIONALE

A comprehensive literature review was performed to identify all studies on prophylactic/suppressive antibiotics after revision shoulder arthroplasty. Searches for the terms "shoulder replacement," "indolent," "infection," "antibiotics," "postoperative" and/or "joint replacement" were performed using the search engines PubMed, Google Scholar and Cochrane review, which were searched through February 2018. Inclusion criteria for our systematic review were all English studies (Level I-IV evidence) that reported on antibiotic prophylaxis, or lack thereof, in cases of revision shoulder arthroplasty. Exclusion criteria were non-English language articles, nonhuman studies, retracted papers, incomplete antibiotic records, case reports, review papers, studies without clinical follow-up/infection rates and technique papers without patient data. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed.

The prevalence of subclinical infections (unexpected positive culture (UPC)) is common after shoulder arthroplasty due to anatomic and demographic factors. In fact, the rate of positive cultures in primary and revision arthroplasty settings have been reported as high as 56% [1–3]. The significance of such cultures remains unknown. There is limited data in the shoulder literature for or against the role for postoperative antibiotics after revision shoulder arthroplasty without clinical or radiographic signs of infection. While several studies described the use of prophylactic or suppressive antibiotics after revision shoulder arthroplasty, there were no prospective randomized studies and none of the studies specifically evaluated efficacy by antibiotic or organism.

Among the published studies for outcomes after revision shoulder arthroplasty with subclinical presentations and unexpected positive cultures, all were retrospective studies with differing methodologies [4–8]. All of the studies reported the majority of positive cultures (> 80%) from indolent organisms (*C. acnes* and/or CNS). None of the studies found a detrimental effect to not prescribing prolonged antibiotics postoperatively, although one study with no comparison group reported a 25% recurrence rate after UPC. One systematic review confirmed a pooled true infection rate after UPC of 10.2%, with antibiotic use not influencing the rate of occurrence of true infection after UPCs (P = 0.498) [9].

Grosso et al. used antibiotic-implegnated cement and 24 hours of routine postoperative antibiotics after revision shoulder arthroplasty and reported 1 superficial infection and no deep infections (91% of organisms cultured were indolent) [4]. Foruria et al. reported 10% persistent infection rate after single stage revision shoulder arthroplasty, although postoperative antibiotic use and positive cultures did not influence the rate of true infections (83% of cultures were positive for indolent organisms) [5]. Padegimas et al. reported a 23.9% UPC rate after revision shoulder arthroplasty with standardized UPC treatment of 6 weeks antibiotics or 2 weeks antibiotics at surgeon discretion. They found only 1 recurrent infection in the UPC group, 3.5% versus 3.4% in the non-UPC group [6]. Kelly et al. reported 8/28 (29%) UPC rate after revision shoulder arthroplasty and only treated one with antibiotics postoperatively for 4 weeks (due to superficial wound infection). Of 8 patients, 2 (25%) developed late clinical infection with *C. acnes* [7]. Lastly, Hsu et al. reported a 49% positive culture rate after revision shoulder arthroplasty and treated patients

based with a protocol of 6 weeks intravenous and 6 months of oral antibiotics if > 2 cultures were positive. Zero percent of patients had recurrence of infection with this protocol in both the positive culture and negative culture groups [8]. On the other hand, the risks of prolonged antibiotic use are significant. Two studies reported a 19-42% complication side-effect rate associated with prolonged antibiotic administration, which was seen in both oral and intravenous medication use [4,8].

The long-term consequences for an unexpected indolent positive culture after revision shoulder arthroplasty are unknown. However, despite lacking randomized comparative methodologies, the literature shows limited evidence that prolonged antibiotic use is not necessary in this scenario. Furthermore, there are well-reported risks of antibiotic-related side-effects and resistance with widespread use.

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3.2. TREATMENT: ANTIBIOTIC FOR PERIPROSTHETIC JOINT INFECTION

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QUESTION 1: Is there a need for antibiotic therapy following irrigation and debridement of patients with acute shoulder periprosthetic joint infection (PJI) caused by a virulent organism (e.g., methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-sensitive *Staphylococcus aureus* (MSSA) or *E. coli*)?

RECOMMENDATION: In the absence of high level data, we propose that patients with acute PJI of shoulder caused by virulent organisms, such as MRSA, MSSA or E. coli, receive postoperative antibiotics. The optimal antibiotic, route of administration and duration of treatment are unknown and should be individualized after consultation with infectious disease specialists.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A systematic review was performed using PubMed and Google Scholar databases in February, 2018 to identify studies regarding the treatment outcomes after shoulder arthroplasty. The keywords included "shoulder AND (replacement OR arthroplasty) AND infection." This search identified 46 articles with relevance to surgical treatment of shoulder prosthetic joint infection, 9 of which described treatment with irrigation and debridement with or without modular component exchange for acute infection (< 3 months from surgery or acute hematogenous spread) [1–9]. These nine studies only included small numbers of patients with only 6 patients with acute PJI caused by a virulent organism [1].

There were no studies identified that directly compared irrigation and debridement versus irrigation and debridement with postoperative antibiotics for the treatment of acute PJI. The nine studies had varied definitions of "acute," with periods ranging from four weeks to three months [1–9]. Data regarding the pathogenic organism was not clearly reported, thus making it difficult to determine whether the virulence was a factor in the treatment or outcome. The surgical management of the acute infections varied, including arthroscopic irrigation and debridement, open irrigation and debridement, and open irrigation and debridement with modular component exchange. Given the limitations of the data, it is not possible to answer the narrow question of whether there is a role for antibiotic therapy in the management of acute shoulder PJI caused by a virulent organism (MRSA, MSSA, *E. coli*) after irrigation and debridement.

Nevertheless, postoperative antibiotics were always part of the treatment of acute PJI in the published literature. Treatment types and length varied; both intravenous and oral regimens were employed, and treatment lengths ranged from 13 days to chronic lifetime suppression [1,2]. Most studies used a four to six-week protocol of postoperative antibiotic therapy [1,3–8]. It appears to be the consensus opinion that acute shoulder PJI treated with irrigation and debridement should be followed by a course of antibiotic therapy. The type, dose and route of administration of the antibiotic should be individualized and determined after consultation with an infectious disease specialist.

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QUESTION 2: Is there a role for antibiotic therapy in the management of acute shoulder periprosthetic joint infection (PJI) with an indolent organism (e.g., *C. acnes* or Coagulase Negative *Staphylococcus*) after irrigation and debridement (I&D)?

RECOMMENDATION: Antibiotic therapy following I&D for management of acute shoulder PJI with an indolent organism has not been well-studied in the literature. The limited data available suggests treatment should consist of antibiotic therapy; however, the optimal antibiotic, route of administration and duration of treatment are unknown.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Treatment strategies for PJI include chronic antibiotic suppression, irrigation and debridement with or without component retention, one or two-stage revision, placement of antibiotic spacer, resection arthroplasty, or arthrodesis. These strategies have been adopted from the hip and knee arthroplasty experience and literature. Most of the data published specifically addressing acute PJI commingles shoulder PJIs with hip and knee PJIs with very little data specific to treatment of acute shoulder PJI alone. The role of antibiotic, the ideal duration or specific antibiotic are not well described. PubMed, Google Scholar, Ovid-Medline, Cochrane and Web of Science were all searched for the following keywords: "shoulder," "infection," "periprosthetic," "arthroplasty," "antibiotic" to identify relevant articles through a title screen, abstract review and, finally, a full text review to identify the relevant manuscripts.

After an extensive review of the literature, we identified a case series of 10 shoulders in 9 patients treated with I&D and antibiotics for acute PJI.

In 2017, Dennison et al. [1] published a retrospective case series of acute PJI treated at the Mayo clinic. They defined acute PJI as any infection requiring I&D within 6 weeks of the index arthroplasty or within 3 weeks of symptoms from a delayed-onset acute hematogenous infection. Anything outside of this time frame was excluded.

They found 10 shoulders in 9 patients with 4 acute postoperative and 6 delayed-onset acute hematogenous infections. Five of the shoulders had a positive culture for indolent bacteria, the other 5 cultured more virulent bacteria. No patient underwent component exchange. The postoperative antibiotic treatment ranged from 3 to 6 weeks with a mean of 5.2 weeks. Antibiotics were determined by an orthopaedic infectious disease specialist based on organism susceptibility and host factors. Nine of the 10 shoulders underwent additional oral antibiotic therapy, which included trimethoprim-sulfamethoxazole with or without rifampin, penicillin or a combination of trimethoprim-sulfamethoxazole with penicillin. Chronic suppression was maintained in 6 shoulders. Of the 10 shoulders, 3 had failure requiring resection arthroplasty. The authors concluded that I&D with antibiotics allowed component retention in 70% of patients treated for acute PJI, although nearly all were prescribed chronic antibiotic suppression.

No studies reported on duration of therapy specific to acute shoulder PJI caused by indolent organisms. Publications reporting on acute shoulder PJI caused by both virulent and indolent organisms describe a wide duration of therapy from 2 weeks to 3 months with poorly described "additional" periods of antibiotics or indefinite therapy. There is conflicting literature regarding the importance of combining therapy with rifampin.

Given the limited nature of the data available, the exact role and protocol for antibiotic treatment after I&D for the treatment of acute shoulder periprosthetic joint infection caused by indolent organism remains unclear. Further studies are required to determine the optimal treatment. Nevertheless, postoperative antibiotics are traditionally prescribed as part of the treatment of acute PJI. Treatment types and length varied; both intravenous and oral regimens were employed, and treatment lengths ranged from 13 days to chronic lifetime suppression [1,2]. Most studies used a four to six-week protocol of postoperative antibiotic therapy [1,3,4]. By consensus we believe that cases of acute shoulder PJI treated with irrigation and debridement should followed by a course of antibiotic therapy.

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QUESTION 3: Is there a role for nonoperative suppressive treatment in the management of subacute or chronic shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: Although there is a role for suppressive antibiotic treatment of selected cases of periprosthetic infection of the shoulder, there are only a few shoulders included in the published literature. The vast majority of published cases describe initial irrigation and debridement, and these are not well separated in the literature from the small number of cases of patients treated with antibiotics alone. No patient treated with antibiotics alone for shoulder PJI has had antibiotics stopped and remained infection-free, thus concerns related to efficacy, long-term toxicity and development of resistant strains are paramount with this strategy. No recommendations can be given on indication, type and duration of suppressive antibiotic treatment.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 0%, Abstain: 4% (Unanimous, Strongest Consensus)

RATIONALE

A literature search (Medline, PubMed) was performed including terms "periprosthetic infection," "PJI," "shoulder arthroplasty," "suppressive treatment," "chronic antibiotic treatment," "ICOAS" to identify studies on suppressive treatment of periprosthetic joint infection of the shoulder. The vast majority of published studies are retrospective, and in total eight shoulder cases were identified (five successful, three failures). Most studies reported on suppressive antibiotic treatment after initial surgical procedure like debridement or emptying abscesses.

Five studies, evaluating suppressive antibiotic treatment included cases of infected shoulder arthroplasty (eight shoulders). Prendki et al. [1] reported on 38 patients with a minimum suppressive treatment of 6 months for a periprosthetic infection (24 hips, 13 knees, **1 shoulder**). Sixty percent of the patients were on antibiotics and without relapse of infection (including the shoulder) at 24 months. There were six failures and nine deaths. Some of these patients had a surgical procedure before initiating suppressive treatment. It is unclear how many patients that were treated without initial surgery.

Wouthuyzen-Bakker et al. reported on a retrospective study of 21 patients (**2 shoulders**) with median follow up of 21 months [2]. They reported 90% success if the patients had a standard prosthesis but only 50% success in patients with a tumor prosthesis. One shoulder case was successful and one was a failure. Only six patients were treated without initial debridement and four had a successful outcome.

Pradier et al. [3] reported on 78 patients (**2 shoulders**) treated with oral tetracyclines as suppressive treatment with a minimum follow up of 2 years. All patients had surgical debridement. Twenty-two patients failed to respond to treatment. Both shoulders were failures. Three cases had acquisition of tetracycline resistance of the initial pathogen.

Prendki et al. [4] reported on a larger series of joint infections, 136 patients. Seventy-nine (58%) had some type of initial surgical procedure. There were **2 shoulders** and both were successfully treated with suppressive antibiotic treatment. It is unclear whether these 2 patients had initial surgery. Prendki et al. also reported on 21 patients (2017) in another study including **1 shoulder** (successful). Of these 21 patients, 5 had fistulas before starting chronic suppressive antibiotic treatment. Forty percent of the patients were free of clinical signs of infection after 2 years [4].

Multiple other studies have included PJI of other joints, primarily hip and knee arthroplasty.

Segreti et al. [5] reported on prolonged suppressive treatment in 18 patients (12 knees and 6 total hip arthroplasties). Eight had acute infection and 10 had chronic infection. All had surgical debridement before antibiotic treatment. Duration of oral antibiotic suppressive treatment varied from 4-103 months. Overall 14 patients remained asymptomatic. Twenty-two percent of the patients had complications related to antibiotic treatment. The authors concluded that suppressive treatment can be an alternative for patients who cannot or will not undergo major surgical revision.

Rao et al. [6] reported on 36 patients (15 hips, 19 knees and 2 elbows). Fouty-seven percent had acute onset (less than 4 weeks) and 53% were chronic infection. All patients had open debridement. Mean duration of treatment was 52.6 months (range 6-128 months). They reported favorable results (retention of a functioning prosthesis) in 86% with a mean follow up of 5 years. Eight percent had complications related to antibiotic treatment.

In 2004, Pavoni et al. reported on 34 patients (again, no shoulders included) with infection. Fourteen had surgical debridement [7]. Seventeen patients had no relapse of infection during the time of this study (11 of these patients had no initial surgical debridement).

Siqueira et al. [8] reported on 92 patients (no shoulders). They compared patients undergoing surgical debridement followed by a short period of antibiotics to prolonged suppressive antibiotic treatment. The five-year infection-free prosthetic survival rate was 68.5% for the antibiotic suppression group compared to 41.1% in the non-suppression group. Hip infections had lower rate of failures, and the suppression group results were better, if there was a *Staphylococcus aureus* infection.

Shelton et al. [9] reported a case of curing of a draining sinus tract in a hip infection. After suppressive treatment the patient discontinued antibiotic treatment and had no relapse of infection or fistula for a period of 8 years.

In summary, a review of the literature demonstrates that there is role for suppressive treatment in periprosthetic joint infection in the hip and knee in patients with stable implants and that cannot,

or do not want, major revision surgery. However, the studies include heterogeneous cohorts of patients with acute, subacute and chronic infections, and the duration and type of treatment varies. Most of the published case series include patients that had long term suppressive antibiotic treatment after an initial surgical irrigation and debridement. It is difficult to identify and evaluate outcome for the patients that only had chronic suppressive treatment. Furthermore, only a few shoulders are included, and, therefore, no recommendations can be given regarding type and duration of suppressive antibiotic treatment for periprosthetic infection in the shoulder. It is difficult to extrapolate from hip and knee infection data, since the clinical manifestation and type of pathogen are different in the shoulder compared to hip and knee. Lastly, profound concerns regarding antibiotic stewardship and antibiotic-related complications must be carefully weighed against any perceived potential modest success of this strategy.

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QUESTION 4: Is there a role for oral suppressive antimicrobial therapy in the setting of retained prostheses after intravenous therapy in subacute or chronic periprosthetic joint infection (PJI)?

RECOMMENDATION: The administration of oral suppressive antimicrobial therapy may have a role in management of patients with chronic or subacute PJI who cannot undergo further surgical intervention.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Many cases of PJI can be managed by means of an adequate medical-surgical strategy with antibiotic treatment administered for a finite period of time. For patients with a PJI, where the medical-surgical treatment is suboptimal or clearly insufficient to achieve control (because of surgical contraindications, technical difficulties, severe medical comorbidities or multi-drug resistant bacteria), chronic oral SAT is considered an alternative strategy.

SAT refers to the use of antibiotics administered indefinitely with a "non-curative" intention and the objective of avoiding or reducing the symptoms and delaying or preventing the progression that may lead to patient dysfunction and the loss of the implant.

A search of Medline and Embase from 1980 to January 2018 was conducted. The terms used were: prosthetic joint infection or infected arthroplasty and suppressive therapy or suppressive antibiotics. Case reports, reviews and guidelines were excluded. Thirteen articles were finally reviewed. When the search was performed including the term "shoulder arthroplasty" or "prosthetic shoulder" and "suppressive antibiotic therapy" or "suppressive antibiotics" no articles specifically on this topic were found. However, a search in medical literature (Medline and Embase) about prosthetic joint infection or arthroplasty and suppressive therapy or suppressive antibiotics yielded 13 references [1–13]. Twelve are retrospective descriptive series, and one is a propensity score controlled cohort study [9]. The vast majority of the cases contained in these series were hip and knee infections, and only 9 of the 680 were prosthetic infections. Therefore, the present review is based on the results obtained with prosthetic hip and knee infections for shoulder prostheses.

Efficacy of SAT varied from 23% at 3.5 years [2] to 86.2% at 5 years [4]. Nonetheless, these wide discrepancies are explained by the use of different criteria in selecting patients for SAT and in defining the response to treatment. The case mix of patients in whom SAT has been prescribed includes a wide spectrum of situations: from acute PJI cases that could probably be cured by debridement and several weeks of antibiotic therapy, to patients with evident chronic infections showing active fistula and no surgery performed.

In summary, the analysis of the literature on SAT faces the following major problems:

1. Different classifications of the PJIs and the terms that are used to describe them (early, acute, delayed, chronic, subacute and so on).
2. Differences in the used medical-surgical strategies as standard of care of the PJI according to the types of infection.
3. Differences in the criteria used to select patients for SAT.
4. Differences in the criteria used to evaluate the efficacy of SAT.
5. Absence of control groups to compare the efficacy of SAT.

As well as other "minor" problems:

1. Insufficient follow up.

2. Variety of antibiotics used.
3. Small sample sizes, in general.

Thus, it is difficult to determine the effectiveness of SAT, although some evidence can be obtained by indirect means. In a cohort of 112 cases with PJI (52 hip, 51 knee, 4 elbow, 3 ankle, 2 shoulder—most of them diagnosed with early PJI, but also including late infections) managed with debridement, prosthesis retention and prolonged antimicrobial therapy for more than a year, the rate of failure among patients that discontinued antibiotic treatment was 4-fold higher than those who continued [7]. Although 82% of the patients who stopped antibiotics did not fail (probably the infection was actually eradicated), the occurrence of failure in some of them indicates that a proportion of those who were not cured by this strategy benefitted from SAT. Failures mainly occurred within the first four months of antibiotic withdrawal.

Another more recent study is the only one that included controls [9]. Ninety-two patients receiving SAT (71 hip PJI and 51 knee PJI) were compared by a propensity score (based on age, sex, type of prosthesis, type of surgery, Charlson index, number of previous revisions and microorganisms) with 276 controls in which clinicians did not administer SAT. The decision to use SAT was individualized, but it is presumed that it was due to "high risk of failure." In fact, 67% of the patients had undergone prior revision surgery. Thirty-six of the cases were "early" PJI and 56 were "late" PJI (no definition of "early" was provided). Cases were managed either by a two-stage revision (38) or by debridement and exchange of polyethylene (54) followed by intravenous antibiotics before SAT was started. A significantly better result was observed in SAT treated patients than in controls (68.5% vs. 41.1%; $p = 0.08$) at 5 years. When analyzed by type of surgery the differences were clear among those managed by prosthesis retention (64.7% vs. 30.4%; $p < 0.001$) but they were not observed in those managed by two-stage exchange ($p = 0.13$). The proportion of success among patients with "late" infections was 64.3%. One of the drawbacks of the study was the fact that the authors included as failures any death during the first year, and the occurrence of severe pain during the follow-up, making it difficult to assess the proportion of true failures because of a lack of infection control.

Interestingly, most series show reassuring data about the safety of long-term antibiotic administration [4,6,10,11,13]. Those who did not tolerate the first selected agent usually tolerated an alternative [12].

In summary, there seems to be some evidence that SAT benefits patients at high risk of failure of prosthesis retention. The main problem is to select in which patients the risk is high enough to compensate for the inconvenience of long-term antibiotic use.

The following conditions also need to be met when considering SAT:

1. Identification of the microorganism that is causing the infection.
2. Availability of oral antibiotics that are not toxic when administered over long periods of time.
3. Practicality of a close follow-up of the patient.

Bearing all these considerations in mind and also the antibiotic stewardship and resistance implications of long-term antimicrobial therapy, the SAT is only indicated after a careful risk-benefit analysis. The temptation to use this strategy to avoid the need for complex but potentially eradicative surgery should be resisted.

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QUESTION 5: Is there a role for oral suppressive antimicrobial therapy in acute periprosthetic joint infection (PJI) in the setting of retained prostheses after initial intravenous (IV) therapy? Same duration as for lower extremity arthroplasty? Should it differ by pathogen (e.g., methicillin-sensitive *Staphylococcus aureus* (MSSA) vs. methicillin-resistant *S. aureus* (MRSA))?

RECOMMENDATION: While the role of debridement, antibiotics and implant retention (DAIR) in the treatment of acute prosthetic shoulder infection has not been well-studied, there is likely a role for oral suppressive antimicrobial therapy in the setting of retained infected shoulder prostheses after DAIR. There is no evidence to guide the optimal duration of treatment or if treatment should vary by organism.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 0%, Abstain: 4% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive systematic review was performed using MeSH terms: "(Arthroplasty, Replacement, Shoulder OR Shoulder joint) AND (Infection OR Debridement OR Anti-Bacterial Agents OR keyword "acute," OR "infection," OR "antibiotics") using Ovid-Medline. The inclusion criteria for this systematic review were English language, shoulder arthroplasty studies that included patients who underwent treatment for periprosthetic shoulder joint infection using irrigation and debridement with component. Exclusion criteria were non-English language articles, technique papers, non-human studies, studies that only presented data on one-stage or two-stage revision, hip or knee arthroplasty articles. Our initial search produced 288 abstracts; 260 were excluded, because they did not fit inclusion criteria, and the remaining 18 manuscripts were obtained and reviewed to assure inclusion criteria. Additionally, the references of these manuscripts were reviewed to ensure no additional relevant material would be missed.

The treatment of an acute hip or knee PJI following irrigation and debridement with implant retention includes a course of oral antibiotics that follows the IV antibiotic therapy [1–3]. Although the efficacy of this approach is debated, with reported success rates ranging from 0% to 89% [4], the use of oral antibiotics (for varying durations) in patients with retained hardware has been reported to be nearly universal, especially in the United States [5]. An analogous algorithm of treatment has been advocated in the setting of acute shoulder PJI when treated with irrigation and debridement with implant retention [6–8], although specific recommendations regarding route and duration of antibiotic therapy are not clear [9,10].

There is very little published literature evaluating the efficacy of this course of treatment in shoulder PJI. Most studies addressing the treatment of acute shoulder PJIs are retrospective case series without control cohorts [11–28]. As many of these studies were comprised of patients undergoing heterogeneous treatment protocols, the subset of patients undergoing DAIR is often only a small subset further limiting the ability of these studies to provide useful data. The overall number of patients presented in these articles is also very small; no study exceeded 50 shoulders and the majority reported on the outcomes of less than 10 patients with acute shoulder PJIs treated with irrigation and debridement and implant retention followed by IV and then oral antibiotics. Details regarding antibiotic use and duration are not always presented or correlated with clinical outcomes. Given the small number of overall cases to draw from, it is difficult to make any inferences regarding the efficacy of this treatment as stratified by organism, including MRSA versus MSSA. Complicating any synthesis of the data further is that patients reported in these studies also varied as to the type of infected arthroplasty (anatomic total shoulder, reverse total shoulder or hemiarthroplasty). Extrapolating these results to assess the actual utility of oral suppressive antimicrobial therapy in acute PJI in the setting of retained prosthesis after initial IV therapy is not feasible nor is it possible to establish a recommended optimal duration of therapy.

Whether DAIR is even a viable treatment approach for shoulder PJIs in any setting has been challenged [10]. A systematic review of the literature published in 2016 found that the failure rate of implant retention in the setting of prosthetic shoulder infection was 31.4% versus a 6.3% failure rate following a two-stage exchange, a 9.7% failure rate following explantation with placement of permanent spacer, and 9.9% following a one-stage exchange [29].

However, despite the lack of supporting medical literature, the use of oral antibiotics, based on the more extensive experience with the treatment of hip and knee infections following debridement as well as the current understanding of the role biofilm plays in treatment failure [25,30–32], is likely a reasonable approach for the treatment of acute prosthetic shoulder infections when treating with implant retention, at least until more rigorous outcomes data that supports the contrary is available.

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QUESTION 6: Should the duration of oral suppressive antimicrobial therapy differ by pathogen (e.g., methicillin-sensitive *Staphylococcus aureus* (MSSA) vs. methicillin-resistant *S. aureus* (MRSA)) in the treatment of subacute or chronic shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: There is insufficient evidence to determine whether the duration of oral suppressive antimicrobial therapy should differ by pathogen in the treatment of subacute/chronic shoulder PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

There is currently no widely shared and commonly used definition of the term "suppressive antimicrobial therapy" (SAT) in reference to antimicrobial therapy for shoulder PJI. A thorough search of PubMed, Embase and Google Scholar databases was undertaken in February, 2018 to identify articles related to the use of suppressive antibiotic therapy for the treatment of shoulder PJI using search terms: "prosthetic joint infection," "suppressive therapy," "antibiotic suppressive therapy," "suppression."

From the results of this search, it is clear that the term SAT is used in various ways. It is often used to mean prolonged antibiotic therapy following surgery (irrigation and debridement and implant revision) with the intention of effecting a cure and discontinuation of antibiotics. In other cases, SAT is described for the treatment of active PJI in patients unable to undergo additional surgical intervention. Treatment in this scenario is palliative; it is based on the principle that organisms within a biofilm cannot be fully eradicated and that the antimicrobial inhibits the organisms in the biofilm from spreading. This may halt dissemination of the infection and prevent sepsis but is highly unlikely to eradicate the underlying infection. Suppressive antibiotic therapy is also used to define indefinite or life-long use of antibiotic therapy in patients without clinical evidence of active infection but thought to be at high-risk for relapse.

Using an inclusive definition of "suppressive antimicrobial therapy," twelve relevant studies were identified [1–8]. From these studies, 34 patients were noted to have had shoulder PJI and received SAT. Failure was defined as a relapse of infection based on the criteria described in each manuscript. These criteria were not consistent. Collectively, patients prescribed SAT had a PJI relapse rate of 29% (10/34 cases). There was not sufficient level of detail to comment on treatment duration, dose of antibiotics or type of antibiotics.

There is some support for success after discontinuation of SAT. Antimicrobial-free periods are not reported in any of the reported series. Reports of hip and knee PJI demonstrate that there is a relapse rate of around 30% within 4 months when suppressive antibiotic treatment is discontinued, even after a long period of suppressive therapy [7]. A study 24 patients with PJI (2 shoulder patients) did observe that treatment succeeded in almost all patients with a PJI caused by a *S. epidermidis* [1]. This finding may not be surprising since *S. epidermidis* has low virulence and the natural course of infection is often dormant and low-grade in nature.

Safety issues in the setting of SAT are an important consideration. Although information is very scarce, the safety data in the published case series indicate a low rate of antibiotic withdrawal due to adverse events [4,7,9].

Moving forward, it may be useful for clinicians and researchers to more precisely define "suppressive antibiotic therapy." The authors would suggest that SAT refer to "the chronic use of low-dose antibiotic therapy in patients with persistent PJI in which the aim is no longer to cure, but to prevent acute exacerbation or recurrence of local symptoms and/or greater systemic involvement." The key to this definition is the recognition that antibiotic therapy is not curative anymore in its intent. Suppressive antibiotic therapy is thereby differentiated from longer-than-standard "prolonged" administration of antibiotics meant to eradicate infection and cease after the infection is deemed to be cleared. Differentiation of these terms may allow future investigators to make more concrete recommendations regarding the use of SAT in shoulder PJI.

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QUESTION 7: What are the recommendations for the route (intravenous (IV) vs. oral (PO)) and duration of postoperative antibiotic treatment when a one-stage revision arthroplasty is performed for subacute or chronic shoulder periprosthetic joint infection (PJI) of the shoulder caused by an indolent organism (e.g., *C. acnes* or coagulase-negative Staphylococcus)?

RECOMMENDATION: Prior to identification of pathogenic organisms from intraoperative cultures, a course of oral antibiotics may be initiated that covers the potential organism until intraoperative cultures are finalized. If the cultures are positive and periprosthetic infection is diagnosed, then a continued course of antibiotics (up to six weeks) should be pursued. There is no evidence to support a preferred route (PO vs. IV), type and duration of antibiotic treatment.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Periprosthetic shoulder infection negatively impacts the outcome of shoulder arthroplasty and is often treated with revision surgery [1]. The overall rate of infection after shoulder replacement is reported as 1.2-3.0% (0.5-3.9% for anatomic and up to 10.0% for reverse shoulder arthroplasty) [2–4]. Prosthetic shoulder infection commonly presents as painful arthroplasty and often lacks typical clinical findings of acute infection. Laboratory workup, such as inflammatory markers, white blood cell count and shoulder aspiration are usually negative, leaving clinicians with limited tools to confirm infection prior to revision surgery. This is mostly due to predominance of indolent organisms, such as *Cutibacterium acnes* (formerly known as *Propionibacterium acnes)* (39-66%) and *Coagulase negative staphylococcus* (24-28%) in periprosthetic shoulder infection [5,6]. Two-stage revision including aggressive debridement, antibiotic spacer placement followed by prolonged IV antibiotics was adopted by shoulder surgeons from treatment of PJI of other joints and showed 63-100% success rate in eradicating infection in short to mid-term follow up [7–9]. This approach has many short-comings, including subjecting patients to two operations and spacer complications, such as fracture, dislocation and loss of rotator cuff and bone stock, leading to poor joint function. Recently, one-stage revision has been advocated for low virulence indolent infections. Nelson et al. [10] and Cuff et al. [11] showed similar rates of eradication after one-stage versus two-stage revision arthroplasty. Beekman et al. reported results of single stage revision for infected reverse shoulder arthroplasty and showed at two year follow-up 90% of patients were infection free with a Constant score of 55.6% [4]. George et al. did a systematic review and found that the average Constant score was 51% after one-stage revision which was better than 41% two-stage revision [12]. These studies make a reasonable case for one-stage revision arthroplasty to eradicate indolent infections while preserving the function of the patient's joint, but they have highly variable protocols for type and duration of postoperative antibiotics. To answer the question above we review and summarize the limited evidence around antibiotic therapy following one-stage revision arthroplasty for periprosthetic shoulder infection with indolent organisms.

A PubMed search was conducted with terms arthroplasty, replacement, shoulder (Mesh) and revision which resulted in 120 papers. Abstracts of the papers were reviewed to identify papers reporting one-stage revision for indolent periprosthetic shoulder infection which resulted in 8 relevant articles that are included in this review.

Most authors retrospectively reporting their experience with treatment of shoulder arthroplasty infection incompletely report the antibiotic therapy following revision surgery. This section will review and summarize the current literature on treatment outcome of infected shoulder arthroplasty with specific focus on antibiotic regimen, as incomplete as it may be, including route (IV vs. PO), type and duration.

Grosso et al. [13] retrospectively reviewed patients with no perioperative sign of infection who underwent single stage revision shoulder arthroplasty and postoperatively had at least 1 positive culture and were not treated with an extended course of antibiotics. The majority of the cultures (56%) were *C. acnes* followed by coagulase negative staphylococci (CoNS) (35%). The rate of recurrence was very low (5.9%). Authors suggested unexpected cultures after a seemingly uninfected one-stage revision did not require extended antibiotic therapy.

Padegimas et al. [14] reviewed 117 one-stage revision shoulder arthroplasty with no preoperative concern for infection who were followed for more than 4 years and found that 28 (23.9%) had an unexpected positive culture postoperatively of which 15 (57.1%) were *C. acnes,* and majority were in male patients. They did not identify any predictor for reoperation, but they observed a higher rate of reoperation in patients without unexpected cultures (20.2% vs. 7.1%) but this did not reach clinical significance. In their cohort, 18 (64.3%) patients were treated with IV antibiotics for 6 weeks, and 10 (35.75) patients only received 2 weeks of PO antibiotics. There was only one reoperation among culture positive patients and that was in a patient who did not receive prolonged antibiotics.

Coste et al. [1] reported on the outcome of treatment in 42 patients with infected shoulder arthroplasty with a mean 34 months follow up. They defined infection based on seven criteria including

presence of a sinus tract, elevated serum white blood cell (WBC) count, elevated erythrocyte sedimentation rate, or C-reactive protein (CRP), positive culture including preoperative aspiration, X-ray evidence of implant loosening and positive bone scan, with no further details on how these criteria were weighted in their definition. There were 20 infections following primary arthroplasty and 22 after revision surgery. Thirty patients (71.4%) had subacute or chronic infection. At final follow up, 22 (73.3%) were infection-free, but there was a wide variation in how patients were treated. They were able to obtain antibiotic information in 30 patients and they judged treatment to be inadequate in 15 patients with regards to duration and type of antibiotics. Five patients were treated with antibiotics only, and only two remained infection-free at final follow up (60% failure rate).

Cuff et al. [11] reported their results of 22 patients with infection following hemiarthroplasty (n = 17) and open cuff repair (n = 5) treated with one versus two-stage revision. In their series, *S. aureus* was the most common organism. CoNS (n = 3) and *C. acnes* (n = 1) were also identified. None of their patients had recurrent infection at mean follow up of 43 months and there was no difference in any of the outcome measures between one versus two-stage revision. The majority of the patients were given six weeks of IV antibiotics, while patients with no clinical signs of infection and with negative intraoperative histology were treated with two weeks of IV antibiotics. It is not clear what type of IV antibiotics were perscribed.

Keller et al. [15] performed a retrospective study of orthopaedic hardware infection that was treated with debridement and retention of hardware, single-stage revision or without surgery to determine if treatment with six weeks of oral antibiotics alters the rate of success at one year. They only included patients who had two separate positive cultures of the same organism from samples taken with a sterile technique from the same site. Of the 89 patients in their study, 42 (47.2%) were infection-free at one year. Patients with methicillin-resistant *S. aureus* (MRSA) or gram-negative organisms, prior infection at the same site, and higher Charlson comorbidity score were less likely to achieve treatment success. They concluded that patients who were on oral suppression for 3-6 months had a significantly lower recurrence rate but continuing antibiotics beyond 6 months did not have the same benefit. Specifically, *C. acnes* infection (n = 32) was associated with a higher likelihood of treatment success at one year (odds ratio: 5.1, 95% confidence interval: 1.32-19.75).

Piggott et al. [16] reported a retrospective study of surgical and nonsurgical management of 24 patients with *C. acnes* PJI from one center with median follow up of 2 years. They defined definite PJI as two positive *C. acnes* cultures or one positive *C. acnes* culture plus sinus tract, clinical purulence or positive histopathology. Probable PJI was defined as one positive *C. acnes* infection and any suspicious clinical sign of infection. There were 11 (46%) definite and 13 (54%) probable PJI cases. The surgery group included 1 incision and debridement with retention, 4 one-stage revisions, 7 two-stage revisions and 3 spacer placements with no re-implantation. The median duration of antibiotic treatment was 6.3 months (range 1.3-50.7). They showed similar success rates with antibiotics only (67%) versus surgery plus antibiotic treatment (71%) (p = 1.0). Fifteen patients (71%) had rifampin as part of their antibiotic treatment but being on rifampin did not significantly change their outcome (73% vs. 60%; p = 0.61) and 40% of patients who received rifampin had to stop it due to side effects.

Hsu et al. [17] reported a retrospective study of 55 failed shoulder arthroplasty cases without clinical evidence of infection who underwent one-stage revision and compared their outcome at average 4 years between patients with ≥ 2 positive cultures (n = 27) and those with 1 or no positive cultures (n = 28). They reported comparable Simple Shoulder Test scores and reoperation rates. All patients received IV vancomycin and ceftriaxone as prophylaxis. If the index of suspicion for infection was high, the IV antibiotics were continued for 3 weeks until the cultures were finalized. If suspicion was low, the patients were started on oral amoxicillin and clavulanic acid for 3 weeks. If cultures were negative or only one culture was positive, antibiotic was stopped at 3 weeks. If ≥ 2 positive cultures became positive at any point, IV ceftriaxone +/- vancomycin was started and/or continued for 6 weeks. They reported 42% antibiotic side effects in this cohort which was higher than the IV antibiotics group.

Klatte et al. [18] retrospectively reviewed their experience with 26 infected shoulder arthroplasty patients treated with one-stage revision at mean follow-up of 4.7 years (range 1.1-13.3 years). The most common organisms were *Staphylococcus epidermis* and *C. acnes*. The majority of patients (94%) were infection-free at final follow up. Antibiotic therapy was tailored to clinical signs, serial CRP levels and serum WBC count. IV antibiotics were given for a mean of 10.6 days (range: 5-29 days). PO antibiotics were given to 4 patients for 5 days, 8 patients for 14 days and 2 patients for 24 days and stopped when CRP normalized and the wound had healed.

The literature on antibiotic treatment following one-stage revision shoulder arthroplasty for subacute and chronic infection is primarily based on heterogeneous case series with inconsistent definitions for infection, and variable treatment protocols. Shoulder PJI with indolent slow growing organisms, such as *C. acnes* and CNS, often have minimal clinical signs of infection. Thus, the diagnosis of infection is frequently made up to two weeks after the revision has been completed. As a practical approach to management, many clinicians recommend using antibiotics for all revision shoulder arthroplasty surgery pending the final cultures results [19].

There is no consensus on duration and type of antibiotics for this period. Antibiotic treatment after cultures are finalized should be dictated by the clinical index of suspicion for infection, culture results, and risk-benefit analysis of antibiotic side effects. There is no high-level evidence currently available to guide this decision.

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QUESTION 8: What are the recommendations regarding the route (intravenous (IV) vs. oral (PO)) and length of postoperative antibiotic treatment when a one-stage revision arthroplasty is performed for subacute/chronic shoulder periprosthetic joint infection (PJI) caused by a virulent organism (e.g., methicillin-sensitive *Staphylococcus aureus* (*S. aureus*), or MSSA, vs. methicillin-resistant *S. aureus* (MRSA), E. coli)?

RECOMMENDATION: Intravenous antibiotics or intravenous followed by oral antibiotics are both reasonable options for one-stage revision shoulder arthroplasty for subacute/chronic shoulder PJI caused by a virulent organism. As there is no consensus on the route or duration, these treatment parameters should be selected in consultation with an infectious disease specialist.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Single-stage revision shoulder arthroplasty is an option for infected shoulder arthroplasty [1–4]. However, the outcomes depending on the virulence of the organism and the ideal duration and mode of antibiotic (IV or oral) treatment associated with single stage revision for PJI is not known.

For this purpose, a comprehensive search on PubMed and Embase database of all English literature till March 2018 was conducted to query keywords: (shoulder OR 'upper extremity') AND (arthroplasty OR replacement) AND (infection OR infected). A total of 1,434 articles were retrieved by the initial search. After review of the title and abstract of all studies, articles focusing on "management of infection" were extracted for further review (n = 31). After applying final exclusion ("two stage revision," "antibiotic spacer" or "antibiotic suppression") and inclusion criteria ("single stage revision," "antibiotic"), a full text review of the articles was conducted, and 6 articles were selected for final analysis. Articles reporting single stage revision but without any information on antibiotic type and or duration were further excluded (n = 2).

The selected studies for analysis (n = 4) evaluated the role of postoperative antibiotic therapy for single stage revision shoulder arthroplasty for PJI. However, it must be emphasized that these studies did not stratify results by the virulence of the organism. Thus, no firm conclusions regarding treatment according to the virulence of the organism can be made.

Beekman et al. retrospectively reviewed 11 consecutive patients with an infected reverse shoulder arthroplasty who underwent single stage revision arthroplasty [5]. Two of these patients had monobacterial infection with a virulent organism (*Staphylococcus aureus* and *Escherichia coli*). Both of these patients received at least three days of IV antibiotic and were discharged on oral antibiotics, which were continued for at least three months. Ince et al. retrospectively reviewed 16 patients with an infected shoulder arthroplasty (three with identified virulent organisms) that underwent single stage revision shoulder arthroplasty [6]. Three patients (~19%) had undergone revision surgery prior to review. All patients received intravenous antibiotics for mean of 8.6 days (range: 5-14 days) and antibiotics were stopped when the surgical incision had healed and/or infection labs (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and white blood cell (WBC) count) were down trending. No recurrence of infection was reported in 9 patients that were reviewed. Klatte et al. reported their results of single stage revision shoulder arthroplasty for PJI in 35 patients, of which 26 were available for review [7]. Patients received IV antibiotics for a mean of 10.6 days (range: 5-29 days), and 11 patients received PO antibiotics for a mean duration of 12.8 days (range: 5-24 days). There were two recurrences. Cuff et al. retrospectively reviewed 22 infected shoulder arthroplasties of which 11 were treated with single stage revision to reverse shoulder arthroplasty and intravenous antibiotics [8]. Five of the 10 patients had virulent pathogens. Patients received antibiotics for 2 (1 patient) or 6 (4 patients) weeks depending on cultures and intraoperative histology results. There was one recurrence of infection.

There is little evidence regarding the subsequent antibiotic management of subacute and chronic shoulder PJI due to high viru-

lence organisms treated with one-stage revision. IV antibiotics or IV followed by PO antibiotics are both reasonable options. However, there is no consensus on the antibiotic type and duration of antibiotic treatment. Presently, clinical judgement and normalization of infection labs (ESR and CRP) for six weeks, if elevated preoperatively, are helpful in determining the duration of antibiotic treatment.

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QUESTION 9: What is the optimal antibiotic treatment for culture-negative cases with positive clinical, radiographic or intraoperative findings for acute shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: The limited data suggests treatment should consist of an empiric antibiotic regimen recommended by an infectious disease specialist considering the local organism profile.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The incidence of culture-negative PJI ranges from 5 to 34% [1]. The following predefined keywords were used during the search using Medline database: ("culture negative") AND ((prosthetic joint infection OR periprosthetic joint infection) OR (arthroplasty AND infection)). Nine original articles [2–11] and a single systematic review [12] have been published on the topic of culture-negative PJI. However, these studies have addressed culture-negative PJI of knee and hip arthroplasty, but not prosthetic shoulder or elbow infections, and have focused on outcomes of culture-negative versus culture-positive PJI (not on the best treatment). The existing publications indicate that the outcome of a patient with culture-negative PJI is similar to that of PJI with a pathogen identified. In these studies, most of these patients with culture-negative PJI have been treated with glycopeptides, mainly vancomycin. Previous antibiotic use was common in these patients, potentially confounding the ability to culture an organism [13].

In a large multicenter study of the microbial etiology of PJI that included more than 2500 PJI cases in Spain [14], Benito et al. analyzed the microbiology of 42 infections of shoulder arthroplasty (data not published); twenty-eight (66.7%) PJIs were caused by aerobic gram-positive cocci, mainly coagulase-negative Staphylococci, followed by *S. aureus*; nine (21.4%) were due to *Cutibacterium* spp. and another nine (21.4%) to *Enterobacteriaceae*; two cases were caused by *Pseudomonas* aeruginosa; five (11.9%) of the PJI cases were polymicrobial infections.

Given the limited nature of the available data, the antibiotic treatment recommended for culture-negative cases of acute shoulder PJI with positive clinical, radiographic or intraoperative findings remains unclear. It is recommended to work with an infectious disease consultant to arrive at a treatment strategy which includes, in addition to surgical irrigation and debridement with exchange of modular elements, empiric coverage against the most common pathogens of acute PJI. A broad-spectrum antibiotic regimen that covers aerobic gram-positive cocci (including methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci) and gram-negative bacilli, as well as *Cutibacterium* species, could be recommended. The need for antibiotic activity against specific multidrug-resistant microorganisms should be considered according to the patient's clinical and epidemiological background.

Treatment with vancomycin or teicoplanin or daptomycin would cover aerobic gram-positive cocci (mainly Staphylococci), in other words, 67% of infections according to the mentioned data. These antibiotics are also active against *Cutibacterium* spp.; however, a beta-lactam (penicillin or cephalosporins) would probably be more active than vancomycin according to a study of 28 strains of *C. acnes* isolated from shoulder surgery [15]. *C. acnes* is highly susceptible to a wide range of antibiotics, including beta-lactams, quinolones, clindamycin and rifampin [16]. However, resistance is beginning to emerge. Recent reports note an increasing emergence of resistance to macrolides, clindamycin, tetracycline and trimethoprim-sulfamethoxazole [16].

- Aerobic gram-negative bacilli would mainly include *Enterobacteriaceae* and *P. aeruginosa*. Besides of the coverture of aerobic gram-positive cocci (with vancomicin, teicoplanin or daptomicin), adding ceftriaxone would be a good option in order to additionally cover *Enterobacteriaceae*, (if there are no suspicion of mechanisms of *Enterobacteriaceae* acquired

resistance such as extended-spectrum beta-lactamases producing (ESBL) *Enterobacteriaceae*). Ceftriaxone is also very active against *Cutibacterium* spp. If *P. aeruginosa* is a concern, cefepime or ceftazidime (instead of ceftriaxone) should be considered. Meropenem (instead of a cephalosporin) would be an option if ESBL-*Enterobacteriaceae* are suspected; it also has activity against *P. aeruginosa*.

- Clearly knowing the organism and antibiotic susceptibility allows for the selection of an antibiotic which is maximally bactericidal to the specific pathogen and minimally toxic to the patient. However, in lieu of this data, the empirical treatment should be typically administered intravenously; the possibility of a second phase with oral antimicrobial treatment should be evaluated on a case by case basis. Consideration of antimicrobial coverage provided before the culture was taken could help to choose the antibiotic regimen, as the clinician may presume the preoperative antibiotic is effective and, theoretically, is the reason the bacteria did not grow in culture. The role of rifampin is not clear in the scenario of a culture-negative PJI, as it has demonstrated its efficacy only in the staphylococcal infections. Moreover, the emergence of resistance with rifampin is high if it is used without another simultaneous antibiotic to which the pathogen is susceptible, and this cannot be guaranteed in a culture-negative PJI.

Long courses of antimicrobial treatment are recommended for infections of hip (3 months) and knee (6 months) prostheses managed with debridement, antibiotics and implant retention (DAIR) [17]. Based on many observational studies and one clinical trial [18] most patients with acute PJI managed with DAIR may be safely treated for 8 weeks [13]. Available information on this topic refers to prosthetic knee and hip infections, and it remains unclear how this data applies to shoulder PJI, where the microbiology of infection varies compared with hip and knee.

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QUESTION 10: What is the optimal antibiotic treatment for culture-negative cases with positive clinical, radiographic or intraoperative findings for subacute or chronic shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: The limited data suggests treatment should consist of an empiric antibiotic regimen recommended by an infectious disease specialist considering the local organism profile.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A systematic review was conducted in March 2018 using PubMed and Google Scholar databases. Keywords included "shoulder" AND ("prosthetic joint infection" OR "arthroplasty infection") AND ("culture" or "culture-negative"). After title and abstract review, fourteen studies were considered for inclusion; additional references were identified from review of reference lists.

There are no studies that have reported clinical outcomes for culture-negative shoulder arthroplasty infections stratified by antimicrobials utilized. There are limited observational data on empiric antimicrobial treatment options for patients with non-shoulder arthroplasty infections. Antimicrobials for culture-negative infections should be selected in light of suspected organisms and their typical antimicrobial resistance profiles, drug tissue penetration (including bone penetration), bioavailability (if oral antimicrobials are selected), host factors (including comorbidities and allergies) and safety considerations. Prior antimicrobial exposure may inform organisms suppressed from culture growth. Additional considerations include the type of surgical procedure, such as whether hardware is retained or exchanged and the use of antimicrobial-laden cement. In the shoulder, most culture-positive subacute and chronic infections are due to coagulase-negative Staphylococci and *Cutibacterium* species [1–3]. Limited evidence in non-shoulder arthroplasty settings have reported good outcomes with vancomycin [4,5] and cephalosporins [5,6]. Most studies in the non-shoulder literature did not find culture negativity to be a poor prognostic factor [5–11], although one study [12] did find worse outcomes in culture-negative knees treated with irrigation and debridement.

The addition of rifampin may be considered if there is strong suspicion for gram-positive infection, particularly staphylococcal, in the setting of maintained hardware [13]. Synergy in the laboratory has been shown with rifampin for *Cutibacterium* [14]; however, there is insufficient clinical experience on the role of rifampin for the treatment of *Cutibacterium* infection to endorse its use [15]. Rifampin should never be used in monotherapy as resistance rapidly emerges; when employed rifampin should be used with careful monitoring and with full consideration of drug toxicities and drug interactions.

Prior antimicrobial exposure is a strong risk factor for culture-negativity [5,7,16]. When infection is suspected, antibiotics should be withheld prior to surgery whenever possible to reduce the likelihood of culture-negative infection. Whether a single dose of perioperative antimicrobial prophylaxis reduces the yield of organisms in low-burden infection is uncertain; two small randomized studies on hip and knee PJI suggest that a single dose of perioperative antibiotic therapy does not reduce operative culture yield [17,18]. Multiple operative samples should also be collected to increase the overall culture yield and to guard against placing too much emphasis on a single positive culture that, in some cases, may be a contaminant [19,20]. Aseptic inflammation and unusual organisms should also be considered in the differential of the culture-negative infection. In these cases, with concern for infection, pathology may be helpful to identify granulomas or other signs of atypical infection; thus, sending tissue samples for pathology is recommended to assist in properly interpreting any culture results. In the appropriate clinical and epidemiologic context, for example in immunocompromised hosts, and, in the setting of penetrating trauma, fungal and mycobacterial cultures should also be considered.

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3.3. TREATMENT: BONE GRAFT

Author: Michael Khazzam

QUESTION 1: Should bone graft or cement be removed during treatment of acute shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: Unknown. There are no reported investigations to guide the decision-making process regarding how to manage cement and/or autograft bone graft in the setting of shoulder PJI.

LEVEL OF EVIDENCE: No Evidence

DELEGATE VOTE: Agree: 90%, Disagree: 5%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

There is no current literature to guide evidence-based recommendations regarding how to manage autograft bone or cement in the setting of acute infection after primary shoulder arthroplasty. Additionally, it is unknown how or if complete removal of this material is necessary to eradicate shoulder PJI. The goal of surgical intervention in the setting of PJI is to debride any material that may result in persistent infection including surfaces with biofilm. Complete removal of autograft bone or cement at times can be extremely difficult and can result in significant bone loss especially if bone graft was used to reconstruct glenoid bone deficiency. A long stem, cemented, well-fixed humeral stem requires a humeral osteotomy or cortical window for complete cement removal which adds significant additional morbidity to the revision procedure. The significance of retaining these materials is unclear and, in order to avoid the complications that come with complete removal of these materials, investigation is needed to understand the risks associated with incomplete removal of cement or bone graft and the risks of recurrent PJI that are associated with this practice. Additionally, it is unknown whether retention of this material requires a change in the postoperative antibiotic management. Finally, it is also unknown how the species of bacterial pathogen and antibiotic sensitivity profile may influence the successful treatment of PJI. Future investigation is required to answer this question in an evidence-based fashion.

Methods

Systematic review of the literature was performed using MeSH terms: cement and infection and shoulder arthroplasty/ replacement, cement and retention and infection, bone graft and infection and shoulder arthroplasty/replacement using search engines PubMed, Web of Science, and CINAHL. Inclusion criteria for this systematic review were Level of Evidence I-IV, English language, shoulder arthroplasty studies which included patient who underwent treatment for PJI and evaluation of the impact of cement removal and/or autograft bone removal classified as either acute, subacute, or chronic infection. Exclusion criteria were non-English language articles, review papers, technique papers, non-human studies, biomechanics or basic science papers, and articles that discussed only hip and or knee arthroplasty PJI. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were used manage the data of this review. The initial search produced 213 abstracts; all of these were excluded as they did not contain any details or evaluation of the question under investigation. Therefore, there are no current studies to reference the impact or effects of cement removal or autograft bone removal in the setting of shoulder arthroplasty PJI for acute, subacute or chronic infection.

Author: Michael Khazzam

QUESTION 2: Should bone graft or cement be removed in treatment for subacute or chronic shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: Unknown. There are no reported investigations to guide the decision-making process regarding how to manage cement and/or autograft bone graft in the setting of shoulder PJI. An attempt should be made to remove all loose, necrotic and foreign material.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A systematic review of the literature was performed using "MeSH terms:" cement and infection and shoulder arthroplasty/ replacement, cement and retention and infection, bone graft and infection and shoulder arthroplasty/replacement using search engines PubMed, Web of Science, and CINAHL. Inclusion criteria for this systematic review were Level of Evidence I-IV, English Language, shoulder arthroplasty studies which included patient who underwent treatment for PJI and evaluated the impact of cement removal and or autograft bone removal classified as either acute, subacute, or chronic infection. Exclusion criteria were non-English language arti-

cles, review papers, technique papers, non-human studies, biomechanics or basic science papers, articles that discussed only hip and or knee arthroplasty PJI. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were used manage the data of this review. The initial search produced 213 abstracts, all of these were excluded as they did not contain any details or evaluation of the question under investigation. Therefore, there are no current studies to reference the impact or effects of cement removal or autograft bone removal in the setting of shoulder arthroplasty PJI for acute, subacute or chronic infection.

There is no current literature to guide an evidence-based recommendation regarding how to manage autograft bone or cement that was placed at the time of primary shoulder arthroplasty and has become infected. Additionally, what is unknown is how or if complete removal of this material is necessary to eradicate shoulder PJI. The goal of surgical intervention in the setting of PJI to debride any material that may result in retained biofilm that, if not removed, may result in a recurrent infection. Complete removal of autograft bone or cement at times can be extremely difficult and can result in significant bone loss especially if bone graft was used to reconstruct bone deficiency of the glenoid. A long stem cemented well-fixed humeral stem can at times require a long humeral osteotomy or cortical windows for complete cement removal which adds significant additional morbidity to the revision procedure.

The significance of retaining these materials is unclear and investigation is needed to understand the risks associated with incomplete removal of cement or bone graft, and what risks of recurrent PJI are associated with this practice to avoid the morbidity that may come with complete removal of these materials. Additionally, it is unknown how retention of this material requires a change in the postoperative antibiotic recommendations for the type, method of delivery or duration of treatment. Finally, it is also unknown how the species of the bacterial pathogen may influence the successful treatment and risk of recurrent PJI, where some less virulent pathogens (such as *C. acnes*) may be more difficult to eradicate with retention of cement or bone graft because of the slow growing nature. Future investigation related to the impact of type of bacteria can provide data to develop a treatment algorithm for which cases can predictably be successful with retention of cement or graft and for which settings require complete removal of all graft and cement materials.

3.4. TREATMENT: COMPONENT RETENTION

Author: Michael Khazzam

QUESTION 1: Is there a role for irrigation and debridement (I&D) with implant retention when treating acute shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: There is insufficient high-quality evidence to support or discourage the use of I&D with implant retention to treat acute shoulder PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

There is little data demonstrating the outcome or infection-free implant survivorship for the treatment of acute shoulder PJI with I&D and implant retention. To date, there are only 37 patients (38 shoulders) with outcomes following this procedure reported in the literature [1–4]. These studies were all grade IV level of evidence (LOE) retrospective case series and demonstrated a 50% failure rate (defined as continued infection) and requiring additional treatment. Three of four studies treated acute, subacute and chronic infections using this technique, but the sample size was too small to analyze how time of infection influences outcomes [1,3,4]. For example, Jacquot et al. found that 1 of the 2 shoulders classified as chronic PJI, 2 of 4 subacute, and 2 of 7 acute had recurrent infection requiring additional treatment [3].

Dennison et al. was the only study found specifically investigating the efficiency of acute (surgery within 6 weeks following index arthroplasty and less than 3 weeks of symptoms) and "delayed onset/delayed acute" (more than 6 weeks following index arthroplasty with symptoms less than 3 weeks) [2]. This retrospective LOE IV case series examined 9 patients (10 shoulders) and found 3 of 10 had recurrent infection requiring resection arthroplasty (mean follow up 4.1 years range 0.58-12.8 years). The method of I&D varied in this study with 3 performed arthroscopically and 7 open. All of the subjects requiring resection had their I&D performed open; the numbers were too small to perform any meaningful analysis of how this may influence outcomes or infection free survivorship. Additionally, 6 of 10 shoulders were maintained on chronic suppressive antibiotics indefinitely without explanation of why the authors selected this treatment.

Further research will be needed to determine how irrigation and debridement with implant retention plays a role in the treatment algorithm of PJI. Specific attention towards answering the questions regarding the effect of the pathogen and the antibiotic sensitivity profile; surgical approach (open or arthroscopic); timing from presentation and index arthroplasty; need for exchange of modular component parts; and type, duration, and method of delivery of antibiotics will be critical to guide these treatment decisions.

Methods

A systematic review was performed using MeSH terms: "I&D shoulder arthroplasty/shoulder replacement, single staged shoulder arthroplasty/shoulder replacement, implant retention revision shoulder arthroplasty/shoulder replacement, acute infection shoulder arthroplasty/ shoulder replacement" using search engines PubMed, Web of Science, and CINAHL. The inclusion criteria for

this systematic review were LOE I-IV, English language, shoulder arthroplasty studies that included patients who underwent treatment for PJI using I&D with component retention (polyethylene and or glenosphere exchange without stem or baseplate removal was included). Exclusion criteria were non-English language articles, review papers, technique papers, non-human studies, and studies that only presented data on one-stage or two-stage revision, hip or knee arthroplasty articles. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were used manage the data of this review. Our initial search produced 66 abstracts; 61 were excluded, because they did not fulfill the inclusion criteria, and the remaining 4 manuscripts were obtained and reviewed to assure inclusion criteria. Additionally, the references of these manuscripts were reviewed to ensure no additional material would be missed. This left four studies for analysis, only one of which evaluated the role for I&D with implant retention for the treatment of acute shoulder PJI.

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Authors: Jeremy Somerson, William Levine

QUESTION 2: What are the indications for irrigation and debridement (I&D) with component retention in subacute or chronic shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: I&D with component retention alone for subacute/chronic shoulder PJI in the literature is less successful than component explant, but may play a role in select patients.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 0%, Abstain: 4% (Unanimous, Strongest Consensus)

RATIONALE

A systematic review was performed using PubMed and Google Scholar databases in February 2018 to identify studies regarding the treatment outcomes after shoulder arthroplasty. The keywords included "shoulder AND (replacement OR arthroplasty) AND infection." This identified 46 articles with relevance to surgical treatment of shoulder PJI; 10 of which described treatment with debridement and implant retention for subacute/chronic infection.

I&D with component retention for shoulder PJI in the subacute and chronic setting has shown low rates of eradication of infection [1–10]. Of the 51 surgical cases identified in studies with a reported eradication rate, approximately half (n = 24, 47%) were successfully cured with debridement alone. The majority of these successful treatments were from two recent studies that integrated modular component exchange with partial component retention [1,2].

Stone et al. [1] reported on patients with shoulder PJI treated with one-stage partial component exchange compared to patients with one-stage complete hardware removal and two-stage revisions. The greatest success rate was with complete one-stage revisions (96% eradication of infection) compared to only 63% eradication for partial one-stage revisions. The authors concluded that there are some circumstances in which retaining a prosthesis may be preferred (such as well-fixed components), but that the surgeon must be aware of a higher risk of recurrent infection.

A French multicenter study reported on 32 patients who underwent revision for infection after reverse shoulder arthroplasty (RSA); of these, 13 patients underwent debridement, modular component exchange and partial component retention [2]. Only 7 patients (54%) were successfully cleared of infection with debridement alone. However, the 15% complication rate reported with debridement was lower than that reported for resection (33%), one-stage revision (20%) or two-stage revision (36%). The authors propose that initial debridement be considered for primary treatment of infected RSA given that more than half of patients were successfully treated with relatively few complications.

Primary treatment of subacute/chronic shoulder PJI with debridement, irrigation and component retention is an option, particularly in patients in which the risks of more aggressive surgery outweigh the potential benefits. However, patients and surgeons should be aware that the published rate of recurrence is substantially greater with this strategy compared to one- or two-stage revision.

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Author: Richard Page, James Beazley, Nicola Luppino

QUESTION 3: Should modular components be exchanged during irrigation and debridement (I&D) of acute shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: Whilst there is logic in exchanging non-fixed modular components, such as the bearing surfaces, to allow thorough I&D of the entire effective joint space and removal of as much biofilm as possible, there is insufficient literature to provide clear guidance.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A thorough search of the PubMed database for manuscripts addressing the exchange of modular parts during shoulder I&D for acute PJI was undertaken. Five papers were found that recorded if modular components were exchanged [1–5], totalling 53 patients. The pooled infection-free survivorship was 65% in the "modular exchange group" (19/29) versus 58% (14/24) in the "no exchange group" ($p = 0.77$ Fisher's exact test).

Of these papers, three [1,3,5] specified the outcome for patients with acute debridement and retention with and without modular exchange. In total, 10 patients underwent acute debridement and retention of prosthesis without modular exchange with an infection free survivorship of 70% (7/10). Eight patients are recorded as having undergone poly exchange during debridement of an acute infection, with an infection free survivorship of 62.5% (5/8; $p > 0.05$).

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Authors: Richard Page, Scott E. Paxton, Ben Clark, Surena Namdari

QUESTION 4: Should modular components be exchanged during irrigation and debridement (I&D) of subacute or chronic shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: We defer to the response for the Question 5: "Should well-fixed glenoid components be removed during surgical treatment for subacute or chronic shoulder PJI?"

It would seem that the recommendation, although of limited strength, would be for well-fixed components to be removed during surgical intervention for subacute/chronic shoulder PJI. Therefore, it can be extrapolated that modular components, which can be exchanged to remove biofilm with far less morbidity than well-fixed components, should likewise be either exchanged or removed and replaced with an antibiotic spacer.

LEVEL OF EVIDENCE: No Evidence

DELEGATE VOTE: Agree: 95%, Disagree: 5%, Abstain: 0% (Unanimous, Strongest Consensus)

Author: Surena Namdari

QUESTION 5: Should well-fixed glenoid components be removed during surgical treatment for subacute or chronic shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: Based on the higher rate of reinfection with component retention, we recommend removal of even well-fixed glenoid components in cases of single-stage revision for suspected subacute/chronic PJI. Certainly, there may be cases (i.e., high-risk surgical patients) where the patient and surgeon may choose to accept the higher failure rate with component retention in order to avoid surgical morbidity introduced by removing well-fixed components.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive literature review was performed to identify all studies on surgical treatment of subacute and chronic shoulder PJI. Previously, we have performed a systematic review on shoulder PJI treatment. In that study, we searched for the terms "shoulder arthroplasty infection" and "shoulder replacement infection" using the search engines PubMed and Embase through April 2014. Inclusion criteria were titles that specified periprosthetic infection of the shoulder (if "Periprosthetic infection" was mentioned, but no joint was specified, the article was included for further review) and articles pertaining to revision shoulder arthroplasty. Exclusion criteria were duplicate titles, review articles, editorials, technique articles without reported patient outcomes and instructional course lecture articles. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed. For this question, the same search terms were used and the dates between May 2014 and February 2018 were searched in order to update the previous systematic review. The prior systematic review identified 663 titles, and an additional 243 were evaluated for the updated review.

In this updated systematic review, three additional studies were identified that met inclusion and exclusion criteria and added to the data from the prior systematic review by Nelson et al. [1] that involved a search until April 2014. Only the study by Jacquot et al. [2] defined a subset of patients treated for subacute or chronic PJI, and the other studies grouped both acute and chronic cases. Based on the available data (all retrospective), there is clearly a higher failure rate of treatment when components are retained (31.3%) as opposed to exchanged via a one-stage or two-stage procedure (< 10%) [1]. Because of this, one must recommend for treatment of subacute/chronic shoulder PJI with removal of all, even well-fixed, components. However, it should be noted that these studies were all based on retrospective review of patients treated according to surgeon preference, and the features of the particular infections are not well documented (bacteria, antibiotic sensitivity, etc.). It is possible, perhaps even probable, that patients treated with implant retention versus removal may have had different infectious presentations that led the treating surgeon to their chosen approach. Further comparative research is needed on this topic. In addition, there may be cases (i.e., high-risk surgical patients) where the patient and surgeon may choose to accept the higher failure rate with component retention in order to minimize surgical morbidity.

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TABLE 1. Updated systematic literature review

Study	Date	Study Design	# Treated w/ I&D and Component Retention	# Failed Treatment (%)	# Treated w/ One-stage Revision	# Failed Treatment (%)	# Treated w/ Two-stage Revision	# Failed Treatment (%)
Nelson [1]	2016	Systematic Review	35	11	282	28	97	6
Stone [3]	2017	Retrospective Case Series	15	4	45	2	19	4
Marcheggiani Muccioli [4]	2017	Systematic Review	27	8	77	3	98	14
Jacquot [2]	2015	Retrospective Case Series	6	3	n/a	n/a	n/a	n/a
Total			**83**	**26 (31.3%)**	**404**	**33 (8.2%)**	**214**	**24 (11.2%)**

I&D, irrigation and debridement

[2] Jacquot A, Sirveaux F, Roche O, Favard L, Clavert P, Molé D. Surgical management of the infected reversed shoulder arthroplasty: a French multicenter study of reoperation in 32 patients. J Shoulder Elbow Surg. 2015;24:1713–1722. doi:10.1016/j.jse.2015.03.007.
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Authors: Richard Page, Akin Cil, Gokhan Karademir

QUESTION 6: Is there a role for routine exchange of all well-fixed implants in revision shoulder arthroplasty without clinical or radiographic signs of infection?

RECOMMENDATION: Unknown. Even in the setting of possible subsequent unexpected positive cultures, there is sparse literature on the routine exchange of well-fixed implants in revision shoulder arthroplasty.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 0%, Abstain: 4% (Unanimous, Strongest Consensus)

RATIONALE

Periprosthetic shoulder infection is one of the most challenging complications of shoulder arthroplasty [1,2]. The difficulty of diagnosis and treatment is attributed to *Cutibacterium acnes* which is a microorganism with low antigenicity [3]. Unlike knee and hip PJI, laboratory tests may be inadequate for diagnosing indolent infection caused by this agent [2]. The prevalence of *Cutibacterium acnes* has been reported to be as high as 50% of intraoperative cultures obtained at the time of revision surgery for a painful and stiff total shoulder arthroplasty [1]. This determination led to the definition of a new clinical entity: "Unexpected positive intraoperative cultures." Due to the fact that this bacterium is a member of the normal skin flora of the shoulder region, it is unknown whether a positive culture should be interpreted as a contamination or a definitive infection [4,5]. Due to the inadequacy of gram stain and frozen-section, and long incubation time; it is difficult to make a decision regarding implant removal during revision surgery [2]. Moreover, in the case of the well-fixed implants, the explant procedure can be difficult and have associated morbidity [5–7].

There is lack of evidence regarding the role for revision of well-fixed implants in revision shoulder arthroplasty without clinical or radiographic signs of infection [2,8]. In a study by Pottinger et al., [8] it has been reported that implants may need to be removed in patients who have risk factors for positive culture. McGoldrick et al. [9] have suggested single-stage reimplantation in the presence of loose implants. However, the authors have not commented on well-fixed implants. Similarly, Grosso et al. [6] have reported low recurrence with the removal of all components and single-stage reimplantation in the patients with unexpected positive intraoperative cultures. On the other hand, Topolski et al. [10] and Kelly et al. [11] reported high recurrence with the retention of implants. Lutz et al. [12] have evaluated infection with *Cutibacterium acnes* in the patients who underwent osteosynthesis or arthroplasty in the shoulder, knee or hip regions and reported that the absence of sepsis findings could not exclude the infection. The authors emphasized that the removal of the implants was important in the success of the treatment of *Cutibacterium acnes* infection of prosthetic material.

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3.5. TREATMENT: IMPLANT

Authors: Mark Frankle, Jason Hsu

QUESTION 1: What is the optimal implant for treatment of acute periprosthetic joint infection (PJI): reverse total shoulder arthroplasty (TSA), anatomic total shoulder arthroplasty (aTSA) versus hemiarthroplasty?

RECOMMENDATION: The optimal implant for treatment of acute PJI is dependent on the status of the rotator cuff, humeral and glenoid bone stock, and patient factors.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 0%, Abstain: 4% (Unanimous, Strongest Consensus)

RATIONALE

Acute shoulder PJI is most commonly considered to be an infection presenting within 3 months after index arthroplasty as described by Sperling et al. [1]. In this scenario, the surgeon has a number of options in the treatment of acute PJI including antibiotic treatment alone, debridement with or without exchange of modular components, single stage complete exchange, two-stage exchange with antibiotic spacer, indefinite implantation of an antibiotic spacer and resection arthroplasty.

Methodology

Using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines, we conducted a systematic review to identify all studies concerning diagnosis and treatment of "infection" at the time of revision shoulder arthroplasty. We searched for all studies published in English using the terms (("revision" OR "failed") AND "shoulder" AND ("arthroplasty" OR "replacement")) limited to dates between January 1, 1996 and February 3, 2018. A total of 2,354 studies were identified. We reviewed the titles and abstracts of all studies and excluded studies that included patients with shoulder infection without arthroplasty or included patients with arthroplasty of joints other than the shoulder. The reference lists for all included studies were searched for any additional references and three references were added to our list. A total of 42 studies met inclusion criteria and were included in the final analysis. Relevant data were extracted from the selected publications, including stratification of acute/subacute/chronic classification, procedures performed, final implants, reinfection rates and functional/clinical results.

Results are summarized in Table 1. Of 42 studies, 19 stratified acute PJI from subacute/chronic PJI with 20% of included patients (93/459) in the acute category. While there were a fair number of studies that described patients with acute PJI, the types of implants explanted and implanted were not regularly reported or stratified; and, therefore, drawing conclusions regarding reinfection rates and clinical outcomes was limited. Also, a clear obstacle in synthesizing the literature was that no consensus definition for shoulder PJI was utilized by these studies [2], and defining reinfection is highly variable in the literature, making the optimal implant of choice for treatment difficult to determine. It should be noted that this review does not include data based on duration of symptoms which may play an important role in choice of intervention.

Indications for Irrigation and Debridement

Irrigation and debridement (I&D) with component retention or exchange of modular components is often considered a reasonable option in acute PJI. This has variable outcomes in the literature with regards to reinfection rates and clinical outcomes (Table 2) [1,3–12]. When aggregated, these 11 studies report a **42% recurrence rate for acute PJI treated with I&D** (19 of 45 patients). Given this data, the surgeon must weigh the risks of recurrent infection with and morbidity of implant removal. The decision on whether to perform an I&D may also depend on the acuity of symptoms with some studies suggesting low recurrence when performed within 2 weeks of symptom onset, even when the time between index surgery and symptom onset is prolonged [6,12] (i.e., secondary hematogenous infection [13]).

Indications for Reverse Shoulder Arthroplasty

Conversion to reverse shoulder arthroplasty may be preferred to an anatomic implant in cases of rotator cuff deficiency and proximal humeral and or glenoid bone loss [6,14,15]. In the setting of a prosthetic shoulder infection, a thorough debridement is required and often necessitates resection of necrotic and infected tissue for adequate infection control. Both infection and soft tissue loss are associated with poor functional outcomes after revision arthroplasty, and implantation of an anatomic implant may not be able to sufficiently compensate for rotator cuff loss and/or instability [15–17]. A reverse implant may better compensate for soft tissue loss or bony deficiency [15,18] and can improve pain control and functional recovery without a high recurrent infection rate in some studies [4,19–22].

In some reports, treatment with a reverse shoulder arthroplasty as a treatment for failed arthroplasty is associated with sub-optimal functional results and a high rate of complication [23–30]. Therefore, hemiarthroplasty should be a consideration in cases in which minimizing complications and further surgery is a priority [31,32].

Indications for Hemiarthroplasty

In cases of acute PJI in a shoulder with an intact rotator cuff, revision to hemiarthroplasty is also a reasonable option with potentially similar results to reverse arthroplasty in the setting of infection [19,33,34]. In addition, in some cases of substantial glenoid bone loss, recurrent instability of a reverse and patient factors, such as

TABLE 1. Studies stratified by infection, acuity and implant type

Author	Journal	Year	Acuity			Procedure(s)	Final Implant					Reinfection By Implant Type	Functional By Implant Type
			Acute	*Subacute*	*Chronic*		*Hemi*	*TSA*	*Reverse*	*Spacer*	*Resection*		
Achermann	Infection	2013	4	5	7	I&D/partial Single-stage Two-stage	NOT DESCRIBED					1 of 4 recurrence with I&D for acute	No comparison of implant types
Amaravathi	Eur J Orthop Surg Traum	2012	8	22	14	I&D/partial Single-stage Two-stage Resection	2	1	23			unclear reinfection rate, 12 of 44 needed revision	No comparison of implant types
Assenmacher	JSES	2017	1	6	28	Two-stage	19	7	9			5 of 35 recurrence, not stratified by acuity/implant	Pain, FE, and ER similar hemi vs TSA vs reverse ($p = 0.76$)
Beekman	JBJS Br	2010	3	7	1	Single-stage			10	1		3 of 3 recurrence with I&D	Median CM 55
Boileau	JSES	2013	1	2	4	I&D/partial Single-stage Two-stage Resection			8		3	2 of 2 recurrence with I&D, uncertain acuity	Likely reverse only
Braman	JSES	2006	1	2	4	Resection					7	Resection only	Resection only
Buchalter	JSES	2017	NOT STRATIFIED			Two-stage	4	5	10			5 of 19 recurrence, not stratified by acuity/implant	No comparison of implant types
Cheung	CORR	2011	6	0	0	I&D/partial	8	4				2 of 6 recurrence	I&D 'unsatisfactory' in 5 or 12 post op hematoma; no implant types
Coste	JBJS Br	2004	12	6	24	Antibiotics only I&D/partial Single-stage Two-stage Resection	NOT STRATIFIED					2 of 2 recurrence with arthroscopic I&D 4 of 6 recurrence with open I&D - those that were undertaken earlier were successful	No comparison of implant types
Cuff	JBJS Br	2008	NOT STRATIFIED			Single-stage Two-stage			17			No recurrence	Mean ASES 57.0, pain 3.5, SST 4.0

TABLE 1. Studies stratified by infection, acuity and implant type (*Cont.*)

Author	Journal	Year	Acuity			Procedure(s)	Final Implant					Reinfection By Implant Type	Functional By Implant Type
DeBeer	Acta Orthop Belg	2006	NOT STRATIFIED			Resection					7	Resection only	Resection only
Foruria	JSES	2013	NOT STRATIFIED			I&D/partial	45	61	1			10% reucrrence but no stratification	No comparison of implant types
Ghijselings	Acta Orthop Belg	2013	5	7	5	Two-stage Abx spacer Resection			3	6	8	No differentiation between 'early' and 'acute hematog-enous'	Resection patients more satisfied than abx spacer
Grosso	JSES	2012	NOT STRATIFIED			Single-stage	2	7	8			No comparison of implant types	No comparison of implant types
Hsu	JBJS	2016	NOT STRATIFIED			Single-stage	33	14	1			No recurrence in hemi, TSA, or reverse	No comparison of implant types
Ince	JBJS Br	2005	NOT STRATIFIED			Single-stage	15		1			No recurrent in hemi or reverse	Mean CM 33.6, UCLA 18.3
Jahoda	Acta Chir Orthop	2008	1	3	7	I&D/partial Two-stage	NOT STRATIFIED					2 of 6 recur-rent with I&D (mixed acute and subacute)	n/a
Jawa	JBJS	2011	6	14	8	Abx spacer Two-stage	3	2	10	12	1	recurrence in 5 of 28 patients	Reverse: Flexion 74, 5 moderate pain, 5 severe pain TSA/hemi: Flexion 61, 4 mild pain, 1 moderate pain
Jerosch	Arch Orthop Trauma Surg	2003	UNCLEAR STRATIFICATION			I&D/partial Two-stage	NOT STRATIFIED					0 of 2 recurrence with early I&D	n/a
Kelly	CORR	2009	NOT STRATIFIED			Single-stage	1	3	24			No comparison of implant types	No comparison of implant types
Klatte	JBJS Br	2013	4	15	16	Single-stage	19		7			2 of 35 recurrence, acuity unknown	Hemi: CM 43.3 Hemi w bipolar head: CM 56 Reverse: CM 61

TABLE 1. Studies stratified by infection, acuity and implant type (*Cont.*)

Author	Journal	Year	Acuity			Procedure(s)	Final Implant					Reinfection By Implant Type	Functional By Implant Type
Lee	Int Ortho	2017	8	4	0	Two-stage	2		10			No recurrence in hemi or reverse	Pain 2.3, ASES 64.2, CM 66.1
Levy	Orthopedics	2015	NOT STRATIFIED			Spacer				9		No recurrence with abx spacer	Pain 2.0, SST 6.3, ASES 65.8, SANE 54.6
Mahure	Orthopedics	2016	NOT STRATIFIED			Spacer				9		No recurrence with abx spacer	ASES 57
Muh	JSES	2013	NOT STRATIFIED			Resection					22	n/a	n/a
Ortmaier	Eur J Orthop Surg Traum	2014	4	9	7	I&D/partial Two-stage Resection	1		14	1	4	2 of 4 recurrence with I&D in acute 3 of 3 recurrence with I&D in subacute	
Pellegrini	Arch Orthop Trauma Surg	2018	NOT STRATIFIED			I&D Abx spacer				19		no recurrence	CM 38.3, pain 1.5, FE 59.2, Abd 52.5
Rispoli	JBJS Br	2007	NOT STRATIFIED			Resection					18	no report of recurrence	ASES 36, SST 3.1
Romano	Int Ortho	2012	9	21	14	Two-stage Spacer Resection	NOT STRATIFIED					1 of 5 recurrence with I&D	Not stratified "Resection with poorest outcomes"
Sabesan	CORR	2011	8	7		Two-stage			17			1 of 17 recurrence with reverse	Penn 66.4, FE 123, ER 26
Sperling	CORR	2001	4	5	23	I&D/partial Two-stage Resection	NOT STRATIFIED					1 of 2 recurrence with I&D for acute 2 of 4 recurrence with I&D for subacute/chronic	n/a
Stevens	JSES	2015	NOT STRATIFIED			Resection					7	1 of 7 recurrence	n/a
Stine	JSES	2010	0	0	30	Spacer Two-stage	10	1	4	15		0 of 30 recurrence	Inadequate stratification to compare implant types

TABLE 1. Studies stratified by infection, acuity and implant type (*Cont.*)

Author	Journal	Year	Acuity			Procedure(s)	Final Implant					Reinfection By Implant Type	Functional By Implant Type
Stone	JSES	2017	NOT STRATIFIED			I&D/partial One-stage Two-stage	STRATIFICATOIN UNCLEAR					4 of 15 recurrence with I&D, uncertain acuity	
Strickland	JBJS Br	2008	3	7	9	Two-stage	13	5	1			7 of 19 recurrence with two-stage	No comparison of implant types
Themistocleous	JSES	2007	NOT STRATIFIED			Spacer				4		no stratification	n/a
Topolski	JSES	2006	NOT STRATIFIED			Single-stage	NOT STRATIFIED					n/a	n/a
Twiss	Seminars in Arthroplasty	2010	NOT STRATIFIED			Spacer Two-stage	STRATIFICATOIN UNCLEAR					0 of 30 recurrence	n/a
Verhelst	JSES	2011	0	4	17	Spacer Resection				10	11	2 of 21 reucrrence	Inadequate stratification to compare implant types
Weber	Int Ortho	2011	NOT STRATIFIED			I&D/partial Two-stage Resection	NOT STRATIFIED					0 of 1 recurrent for I&D	
Zavala	JSES	2012	5	2	0	I&D/partial Resection			5		2	1 of 4 recurrence with I&D	
Zhang	JSES	2015	NOT STRATIFIED			Two-stage	2	1	15				No comparison of implant types
			Acute	*Subacute*	*Chronic*		*Hemi*	*TSA*	*Reverse*	*Spacer*	*Resection*		
		TOTAL	**93**	**148**	**218**	**TOTAL**	**179**	**111**	**198**	**86**	**90**		
			20%	**32%**	**47%**		**27%**	**17%**	**30%**	**13%**	**14%**		

I&D; irrigation and debridement; TSA, total shoulder arthroplasty

TABLE 2. Success of I&D with component retention or exchange of modular components

Author	Journal	Year	No. Undergoing I&D	No. Recurrent Infection
Achermann	Infection	2013	4	1
Beekman	JBJS Br	2010	3	3
Cheung	CORR	2011	6	2
Coste	JBJS Br	2004	8	6
Jahoda	Acta Chir Orthop	2008	6	2
Jerosch	Arch Orthop Trauma Surg	2003	2	0
Ortmaier	Eur J Orthop Surg Traum	2014	4	2
Romano	Int Ortho	2012	5	1
Sperling	CORR	2001	2	1
Weber	Int Ortho	2011	1	0
Zavala	JSES	2012	4	1
TOTAL			**45**	**19**

noncompliance precluding implantation of a reverse, conversion to a hemiarthroplasty [32] may be the preferred choice to minimize intraoperative and postoperative complications [35].

Indications for Total Shoulder Arthroplasty

While better pain relief and functional scores can be obtained with total shoulder arthroplasty than hemiarthroplasty [36], the rate of polyethylene glenoid component loosening in the setting of revision is high [37]. In the setting of acute PJI, conversion to total shoulder should be strictly limited to cases in which the rotator cuff is fully intact, glenoid bone stock is sufficient, and bacterial burden is minimal.

In select cases, resection arthroplasty [38–42] and indefinite placement of an antibiotic spacer [43–45] can be considered for acute PJI.

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3.6. TREATMENT: RESECTION

Authors: José M. Mora, Simon Lambert

QUESTION 1: What are the indications for resection shoulder arthroplasty in acute periprosthetic joint infection (PJI)?

RECOMMENDATION: There are no available reports on resection shoulder arthroplasty for acute PJI. At this time there is no evidence to routinely recommend this treatment for this indication.

LEVEL OF EVIDENCE: No Evidence

DELEGATE VOTE: Agree: 88%, Disagree: 8%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Search Strategy

A request via the Royal Society of Medicine Library utilizing ProQuest Dialog, searching Embase and Medline archives. Search terms: (excision arthroplasty) OR (resection arthroplasty) AND (acute periprosthetic infection) OR (chronic periprosthetic infection) OR (subacute periprosthetic infection). Yielded 1,649 references. After limiting these to shoulder-specific references and eliminating duplicates 100 references were further searched for exact matching to the question of the role of resection arthroplasty in the management of acute PJI (subacute or chronic PJI). All full papers, reviews and abstracts in English between 1990 and 2018 were examined, and those reporting the indications and outcomes of resection (excision) arthroplasty of the shoulder were examined further. Personal searches of PubMed archives were performed by both authors using the same criteria, and their searches were compared. The bibliographies of two recent reviews (one specifically examining the question of resection, the value of spacers and one-and two-stage revision arthroplasty in subacute or chronic PJI [1], the other a more general review [2]) were examined for further references and cross-checked with the first enquiry and the personal searches.

No manuscripts were identified which reported on resection shoulder arthroplasty for acute PJI.

Conclusion

The available literature has no evidence pertaining to resection arthroplasty in acute shoulder PJI to provide guidance on this question.

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QUESTION 2: Is there a role for resection shoulder arthroplasty in the management of subacute or chronic periprosthetic joint infection (PJI)?

RECOMMENDATION: The available literature does not support specific indications for resection arthroplasty for subacute or chronic shoulder PJI with sufficient quality information to provide guidance. Resection arthroplasty is an acceptable salvage treatment to eradicate shoulder PJI when revision to a definitive implant is considered too risky due to patient medical co-morbidities or technical complexity.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 95%, Disagree: 0%, Abstain: 5% (Unanimous, Strongest Consensus)

RATIONALE

There are no prospective studies or randomized trials on this topic, and all published reports are retrospective case series. In addition, many of these case series include no other cohort to directly compare against any other form of treatment strategy for infected shoulder arthroplasty. The available literature is further limited by the fact that all published series examine outcomes using a variety of methods: (a) pain relief, recorded either as a subset of a score, e.g., the Constant-Murley (CMS) or American Shoulder and Elbow Surgeons (ASES) scores, or as a visual analog scale (VAS); (b) function, recorded either as a subset of a score, or by direct description; (c) management of infection, recorded as either "eradicated," "recurrent" or "persistent" (with no clear definition on how these categories was diagnosed/confirmed).

The systematic review of management strategies for shoulder PJI by George et al. [1] found 8 papers (total number of cases, 83) relating to the use of resection arthroplasty. The number of cases reported per series varied between 5 and 21 with a mean duration of follow-up of post-resection 39.8 months (standard deviation 20.8), minimum 19.2 (9.4), maximum 102.6 (41.9). The number of infections considered eradicated was 72/83 (86.7%) with no difference (statistical or clinically meaningful) in infection eradication observed between resection, single-stage, two-stage and permanent spacer arthroplasty. Preoperative and postoperative functional scores were incompletely reported. Single-stage revision cases had better preoperative scores than other groups, and better outcomes. It should be noted that patients reported worse functional scores (CMS) after surgery than before surgery, particularly for resection arthroplasty. There was no consistency in the choice or duration of antibiotic administration after surgery. Importantly, the authors pointed out that the limited quality of the available literature meant that it was not possible to provide a conclusion concerning the indication for one modality over another if the aim of intervention was to eradicate infection while optimizing the functional outcome for patients.

When reviewing the available literature, it should be noted that the majority of PJI for which resection is reported as an outcome are reverse total shoulder arthroplasties [2–4]. It is not clear whether this relates to the more challenging reconstructions often encountered after revision reverse total shoulder arthroplasty (TSA) or perhaps the nature of the reverse TSA patient population who tend to have more medical comorbidities and lower functional demands.

Patient outcomes including eradication of infection, pain relief and function were reported using variable standards. The concept that resection arthroplasty carries the advantage of being "one final surgery" should be tempered by the results showing that, on average, two debridements were required for infection to be clinically eradicated (mean follow-up 20 months) [5]. Braman et al. [5] showed that in their series of seven patients, while the functional scores were generally poor, all patients were able to perform activities between the mouth, opposite axilla and perineum and were satisfied with the outcome. Other authors, however, have shown that patient satisfaction is poor overall. Rispoli et al. reported one-third of cases falling into the lower third of categories for satisfaction, and 16 of 18 cases having an unsatisfactory outcome by Neer criteria [6]. If preoperative impairment was not substantial (defined as a CMS of greater than 30) then there was no significant improvement after surgery [2]. The same authors considered that reimplantation (whether one- or two-stage) delivered better functional outcomes than resection arthroplasty [2]. Zavala et al. (2012) concluded that resection was inferior to a debridement, antibiotics, irrigation and implant retention (DAIR) strategy in providing for function without increasing the risk of persistent or recurrent infection at a minimum of 12 months follow-up, while also commenting that implant retrieval lead to (potentially) revision-limiting bifocal bone loss [7]. DeBeer et al. recommended resection be indicated for the elderly with PJI and with lower functional expectations [8]. A single comparative study comparing resection with staged reimplantaion demonstrated that there was benefit for range of motion if a staged reimplantation could be safely undertaken with no increased risk of persistent or recurrence of infection [9]. This study was presented at the American Academy of Orthopaedic Surgeons (AAOS) and does not appear to have been published elsewhere. Resection arthroplasty for subacute or chronic PJI may some provide pain relief in approximately one-third to one-half of cases [3,6,7,10–12].

There are some technical and prognostic factors which may effect patient functional outcome and satisfaction. Retention of the tuberosities appears useful for function, possibly by reducing the tendency for proximal humeral migration [12]. In addition, there is some debate regarding how an antibiotic spacer may compare with resection alone with respect to eradication of infection and function. Verhelst et al. reported that use of a spacer (permanent

TABLE 1. Articles specifically concerning resection arthroplasty in shoulder PJI, with details as noted

Author	Year	n	Failed	CMS	SST	Surgery Prior to Resection (N)	VAS	ASES	FE	Abd	ER
Verhelst	2011	11E	2/11	40.4			2.6		85.5°	78.1°	21°
		10 EAS									
Rispoli	2017	18 E			3.1		4.5	36	70°		31°
Stevens	2015	4 E	1/4		3.3	2 cases = 3 2 cases > 5	8.8	20.8	63°		25°
		4 EAS	0		6	1.5	0.4	69	85°		30°
Maynoud	2006	10 E	0	28							
Braman	2006	7 E	0			2.2			28°		8°
Ghijselings	2013	8 E		27.8	2.4		3.6				
		5 EAS		20.6	1		6				

NB: many data are incomplete since not all ideal data were recorded by the authors (see [6]). In three studies there are comparison cases of explantation and antibiotic spacer (EAS) and explantation alone (E) [1,13,14,16].

or temporary) did not appear to compromise eradication of infection but also did not necessarily confer benefit for function or pain relief postoperatively [13]. In contrast, Ghijselings in a comparative series evaluating resection with resection plus antibiotic-impregnated spacer reported a differential benefit for spacer with regard to domestic activities, but overall functional scores and pain relief were no different [14]. In the setting of bilateral pathology, Ueda et al. concluded there is improved function for domestic activities with bilateral retained antibiotic spacers when compared with historical reports of resection arthroplasties for PJI [15].

In summary, the functional result is relatively poor, but the eradication of infection is quite good (86.7%), especially considering that in these non-randomized studies patients with resection arthroplasty are likely frail and/or have difficult to treat pathogens [1]. It remains unclear whether a resection arthroplasty is preferred versus a retained antibiotic-impregnated cement spacer, with some studies suggesting a modestly better functional result with the spacer. Resection arthroplasty is an acceptable salvage treatment when revision to a definitive implant is considered too risky due to patient medical co-morbidities or technical complexity of revision surgery.

Search Strategy

A request via the Royal Society of Medicine Library utilising ProQuest Dialog, searching Embase and Medline archives with search terms (excision arthroplasty) OR (resection arthroplasty) AND (acute periprosthetic infection) OR (chronic periprosthetic infection) OR (subacute periprosthetic infection) yielded 1649 references. After limiting these to shoulder-specific references and eliminating duplicates, 100 references were further searched for exact matching to the question of the role of resection arthroplasty in the management of subacute/chronic PJI (SA/C PJI). All full papers, reviews and abstracts in English between 1990 and 2018 were examined, and those reporting the indications and outcomes of resection (excision) arthroplasty of the shoulder were examined further.

Personal searches of PubMed archives were performed by both authors using the same criteria, and their searches were compared. The bibliographies of two recent reviews (one specifically examining the question of resection, the value of spacers and one-and two-stage revision arthroplasty in subacute/chronic PJI [1], the other a more general review [17]) were examined for further references and cross-checked with the first enquiry and the personal searches. This strategy was compared with that of the most useful review [1] for completeness.

In Stevens et al. [16], there were seven patients available – eight cases (four explantation and four explantation and antibiotic spacer). In mobility there were three cases with data not available. In relation to "failed," there was only one case following explantation alone, which equates to 25% as a proportion of the group, or 12.5% as a proportion of all cases in this series.

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3.7. TREATMENT: REVISION

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QUESTION 1: Is there a role for an antibiotic spacer for the treatment of shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: An antibiotic loaded cement spacer may be used as part of a shoulder two-stage exchange arthroplasty for local delivery of high concentration of antibiotics. An antibiotic loaded cement spacer may be used as a definitive/permanent treatment option in select cases.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Antibiotic loaded cement spacers can be used in the management of infected shoulder arthroplasty [1–4]. The antibiotic loaded cement spacer delivers antibiotics to the local tissues, eliminates dead space, maintains soft tissue tension and shoulder function and is used for these reasons as a temporary spacer in two-stage reimplantation for infected shoulder arthroplasty [2,3]. Less commonly, it can be considered as a permanent/definitive spacer if the patient declines further surgery or if the patient is not a good surgical candidate for the second stage of two-stage reimplantation (e.g., sick patient, significant bone loss) [5–8].

The role of antibiotic loaded cement spacer in shoulder PJI has been studied previously in retrospective cohort studies (Table 1). An antibiotic loaded cement spacer is indicated as a temporary spacer in the two-stage treatment of shoulder PJI in conjunction with intravenous antibiotics [2,3]. However, use as a definite/permanent spacer has also been described as a treatment for patients who are a high surgical risk or refuse second stage of two-stage treatment [5–7]. Jawa et al. reported a retrospective review of 28 patients with infected shoulder arthroplasty who were managed with antibiotic loaded cement spacer [2]. Sixteen patients underwent a two-stage operation, and twelve patients declined second stage procedure. Five patients had recurrence of infection (18%), and 5 patients had severe pain (18%) at final follow up. Complications with the use of cement spacer included dislocation (1 patient) and fracture (3 patients). Torrens et al. reported a culture positive rate of 13.6% (3 shoulders) from 22 antibiotic loaded cement spacers retrieved during second stage reimplantation [9]. In contrast to studies by Jawa et al. and Torrens et al., other investigators have reported lower rates of recurrence of infection with antibiotic loaded cement spacer use. Pellegrini et al. reported no recurrence of infection with a definitive antibiotic spacer in a cohort of 19 low demand, elderly subjects who had infected shoulder arthroplasties [6]. At a mean follow up of 8 years, all patients reported satisfactory subjective and objective outcomes. One patient had glenoid osteolysis with no adverse effect on functional outcome. Levy et al. retrospectively reviewed outcomes in 9 patients with infected shoulder arthroplasty who elected to not have the second stage reimplantation [7]. These patients had acceptable function with their antibiotic spacers at a mean follow up of 25 months. There was no recurrence of infection (0%) and only one patient (11%) was unsatisfied with the results. Mahure et al. reported no recurrence of infection (0%) in a retrospective case series of patients with shoulder PJI who received an antibiotic loaded cement spacer as definitive treatment after first stage of the two-stage treatment [5,10]. In a retrospective study, Romano et al. reviewed 44 patients with infected shoulder arthroplasty of which 32 patients had treatment with a temporary or permanent antibiotic loaded spacer [11]. There was one recurrence of infection in the definitive spacer group. Lee et al. used an antibiotic loaded cement spacer for the first stage implantation in 12 patients with infected shoulder arthroplasty. All patients received intravenous antibiotics followed by the second stage treatment [12]. There was no recurrence of infection (0%) at mean follow up of 41 months. Improved functional outcomes with the use of antibiotic loaded cement spacer was reported by Jerosch et al. in a retrospective review of 10 patients with shoulder PJI [13]. Patients were able to perform physical therapy with the antibiotic spacer in situ, and 8 patients underwent second stage with no reported recurrence of infection.

There is no consensus on the optimal class of antibiotics to be used in spacer preparation. Heat stable antibiotics (vancomycin, gentamycin and tobramycin) have been used alone or in combination. Spacer design and patient-specific anatomic features have also been studied with regards to infection clearance and patient satis-

TABLE 1. Studies examining the role of antibiotic loaded cement spacer in treatment of infected shoulder arthroplasty

Study	Number of Patients / Shoulders (n) and Follow-up (FU)	Antibiotics Used in the Cement Spacer	Spacer Role	Recurrence of Infection and Complications Associated with Spacer
Jerosch and Schneppenheim, 2003	n = 10 FU:6-30 mos (range)	No information	Temporary: 8 Permanent: 2	Recurrence: 0%
Themistocleous et al., 2007	n = 4 FU:22 mos	Tobramycin Vancomycin	Temporary: 2 Permanent: 2	Recurrence: 0%
Coffey et al., 2010	n = 16 FU:20.5 mos	Gentamicin	Temporary: 12 Permanent: 4	Recurrence: 0%
Jawa et al., 2010	n = 28 FU= 27.6 mos	Tobramycin Vancomycin	Temporary: 16 Permanent: 12	Recurrence: 5 (18%) Dislocation: 1 (3.5%) Fracture of spacer: 3 (11%)
Stine et al., 2010	n = 30 FU: 2.4 yrs	Tobramycin Vancomycin	Temporary: 18 Permanent: 15	Recurrence: 0%
Romano et al., 2012	n = 32 FU:2.4 yrs	No information	Temporary: 17 Permanent: 15	Recurrence: 3% (one in permanent group)
Levy et al., 2014	n = 9 FU:25 mos	Tobramycin Vancomycin	Permanent	Recurrence: 0%
Mahure et al., 2016	n = 9 FU:4 yrs	Tobramycin Vancomycin Gentamycin	Permanent	Recurrence: 0% Glenoid erosion: 2 (22%) Periprosthetic fracture: 1 (11%)
Pellegrini et al., 2017	n = 19 FU:8 yrs	Gentamycin, Clindamycin, Vancomycin	Permanent	Recurrence: 0% Glenoid osteolysis (1; 5.3%)
Padegimas et al., 2018	n = 37 FU:4 yrs	Tobramycin Vancomycin	Temporary	Spacer revision: 1 (2.7%) 6 positive cultures at second stage but no clinical signs of infection
Lee et al., 2018	n = 12 FU:40.8 mos	Vancomycin	Temporary: 9	Recurrence: 0%
Torrens et al., 2018	n = 21	Tobramycin	Temporary	Revision of spacer: 1 3 Positive cultures at second stage (13.6%)

faction. Padegimas et al. retrospectively compared stemless and stemmed antibiotic spacers in a cohort of 37 patients with shoulder PJI [14]. They found no difference between the two types of spacers with respect to their ability to control infection and the percentage transition (70% in both groups) to the second stage of a two-stage procedure for infected shoulder arthroplasty. There is insufficient date to compare handmade versus commercial premade antibiotic loaded cement spacers.

An antibiotic loaded cement spacer is a reasonable treatment option as a temporary antibiotic spacer in conjunction with intravenous antibiotics for the two-stage treatment of shoulder PJI. The majority of studies report no recurrence of infection after revision to second stage. Use of an antibiotic loaded cement spacer as a definitive/permanent treatment can be considered for a low demand, debilitated patient who is a poor surgical candidate for second stage reimplantation or in cases where patient refuses second stage surgery. There is low rate of infection (5%) with acceptable functional outcome, but glenoid osteolysis is a concern with the use of cement spacer as a definitive treatment. There is no consensus on the ideal class of antibiotic (vancomycin versus aminoglycosides) to be used in cement spacers. There is insufficient data to compare hand-made versus commercial premade antibiotic spacers.

Search Methods

In order to establish guidelines for the use of an antibiotic loaded cement spacer in infected shoulder arthroplasty, a systematic review of literature on PubMed and Embase was performed of all English

literature till January 2018 to query, "(shoulder OR 'upper extremity') AND (arthroplasty OR replacement) AND (infection OR infected) AND (PROSTALAC OR ANTIBIOTIC SPACER). After excluding duplicates, a total of 34 articles were screened, and 16 studies focusing on use of an antibiotic loaded cement spacer as a temporary or permanent spacer were extracted for further review. After applying final exclusion ("one-stage revision," "antibiotic suppression") and inclusion criteria, a full text review of the articles was conducted, and 12 articles were selected for final analysis. All the articles evaluated the role of antibiotic loaded cement spacer for the treatment of shoulder PJI [2–14].

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QUESTION 2: What are the indications for one- versus two-stage exchange arthroplasty in the management of acute shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: Unknown. Single-stage exchange for shoulder PJI had a statistically significant lower reinfection rate and lower complication rate than two-stage exchange in aggregate; however, no studies exist directly comparing these treatments for acute shoulder PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive literature review was performed to identify all studies on revision shoulder arthroplasty for PJI. Terms used for the search included "infection," "shoulder replacement," "arthroplasty," "1-stage," "2-stage," "reimplantation," "prosthetic-related infection" and included "resection," "spacer" or "exchange" among others using PubMed, Scopus and Embase through February 2018. Inclusion criteria for our systematic review were all English studies (Level I-IV evidence) that reported on single or two-stage revision, infection eradication for revision shoulder arthroplasty with a minimum follow up of twelve-months and minimum of five patients for analysis. Exclusion criteria for our review were all non-English studies, papers that exclude single or two-stage exchange, review papers, case reports or technique articles without outcome data. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were applied. Title and abstract screening was conducted through 248 results; full text review was conducted with 66 results and produced 31 articles that met inclusion and exclusion criteria for review.

Shoulder PJI is a devastating complication with significant morbidity. The incidence of PJI after primary shoulder arthroplasty has reported ranges of 1-4% and up to 4-15% after revision arthroplasty [1,2]. Historically, treatment for shoulder PJI has been influenced by evidence from hip and knee arthroplasty infection management experience [3,4]. Two-stage exchange arthroplasty with implant removal, irrigation and debridement (I&D), and insertion of antibiotic spacer, followed by delayed re-implantation has been suggested as gold standard for shoulder PJI [3]. However, single-stage exchange has also been advocated to achieve similar infection control with a single surgery [5–7]. The purpose for this review was to understand the roles of single-stage and two-stage exchange revision in the setting of acute shoulder PJI and compare the outcomes.

In this review, varying studies collected demographics, timing of infection, associated pathogens, surgical treatment, antibiotics, eradication rate for infection, surgical complications and functional outcomes with two-year follow-up minimum. We identified 12 articles that evaluated one-stage exchange and 27 articles that evaluated two-stage exchange.

While the definition and diagnosis of shoulder PJI is beyond the scope of this review, it should be noted that the majority of papers reported using preoperative laboratory values (including elevated white blood cell count, C-reactive protein (CRP) and/or erythrocyte sedimentation rate (ESR)), as well as joint aspiration and/or intra-

TABLE 1. Reinfection and complication

One-Stage	Patients	Reinfection %	Pathogens	Constant Score	Complications
12 Papers	161 Total	5.6% Reinfection	72 P. acnes	49.1	12.70%
	6 Acute	$p < 0.05$	29 CoNS	44 Patients	79 Patients
	13 Subacute		20 MSSA	$p < 0.11$	$p < 0.05$
	8 Chronic		3 MRSA		
Two-Stage	**Patients**	**Reinfection %**	**Pathogens**	**Constant Score**	**Complications**
27 Papers	325 Patients	11.4%	88 P. acnes	51.1	21.90%
	47 Acute	$p < 0.05$	64 CoNS	102 Patients	205 Patients
	46 Subacute		33 MRSA	$p < 0.05$	$p < 0.05$
	74 Chronic		56 MSSA		

operative cultures with bacterial growth to arrive at the diagnosis of shoulder PJI. Clinical findings, such as draining sinus, erythema or swelling, were inconsistently reported. There was inconsistent reporting and definition of the timing of infection as acute, sub-acute or chronic. The majority of studies report timing of infection using terms from Sperling et al. and Strickland et al. with acute meaning < 3 months, sub-acute meaning 3-12 months and chronic > 12 months [8, 9]. There was relatively consistent reporting of the pathogens found either pre- or intraoperatively. *Cutibacterium acnes* (*C. acnes*) was the most common organism identified with 160 cases or 32.9% of all cases followed by *Coagulase-negative Staphylococcus* (CoNS) with 93 cases or 19.1% [2,4,7–15]. There were 57 reported cases of poly-microbial infections and 27 cultures that resulted in no growth [4,7,10–12].

To address the stated question, we reviewed data on acute shoulder PJI pertaining to infection eradication using single or two-stage exchange and additional functional outcomes, which are summarized in Tables 1 and 2. In total, 161 cases were identified as treated with single-stage revision and 325 cases of two-stage revision. The majority of studies report timing of infection but few report the success of treatment with either single or two-stage exchange based on timing of infection. Beekman et al. performed analysis on three cases of acute PJI treated with single-stage exchange showing no cases with reinfection [5]. Two additional studies with a total of three cases of acute PJI found no patients had reinfection [6,10]. With two-stage exchange, Buchalter et al. [16] described 1 case of acute PJI that had no reinfection. Another study reported 1 case of acute PJI that failed treatment with two-stage exchange and had persistent infection. In total, four studies reported no cases of reinfection with two-stage exchange with specific analysis of an acute PJI subgroup.

This review has highlighted gaps that exist in current literature. All studies identified were retrospective and thus have substantial selection bias. While the findings in aggregate suggest single-stage exchange is a viable option for PJI, the numbers were small, and there are no studies that control for various risk factors and selection biases such as the particular pathogen, its antibiotic resistance profile, timing of infection or diagnostic features such as obvious clinical findings of infection. Furthermore, there are insufficient numbers of studies that provide analysis for treatment of acute

TABLE 2. Functional outcome

One-Stage	Neer (total)	ASES (mean)	SST (mean)	DASH	FF (mean)	ABD (mean)	ER (mean)
12 Papers	1,7,2	60.5	7.8	N/A	78.2	52.4	25.4
	10 Patients	50 Patients	27 Patients	None	57 Patients	42 Patients	59 Patients
Two-Stage	**Neer (total)**	**ASES (mean)**	**SST (mean)**	**DASH**	**FF (mean)**	**ABD (mean)**	**ER (mean)**
	22,33,32	67.6	4.1	57.7	98.9	52.4	29.2
	87 Patients	101 Patients	32 Patients	15 Patients	194 Patients	72 Patients	144 Patients

shoulder PJI using either single or two-stage exchange with regard to complications or functional outcomes.

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QUESTION 3: What are the indications for one- versus two-stage revision in subacute or chronic shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: The indications for one-stage versus two-stage exchange are unclear at this time. The pooled data demonstrate one-stage exchange to be superior to two-stage exchange, but this may be a result of selection bias and other factors.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 0%, Abstain: 4% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive literature review was performed to identify all studies on revision shoulder arthroplasty for periprosthetic joint infection (PJI). Terms used for the search included "infection," "shoulder replacement," "arthroplasty," "1-stage," "2-stage," "reimplantation," "prosthetic-related infection" and included "resection," "spacer" or "exchange" among others using PubMed, Scopus and Embase through February 2018. Inclusion criteria for our systematic review were all English language studies (Level I-IV evidence) that reported on single or two-stage revision, infection eradication for revision shoulder arthroplasty with a minimum follow up of twelve-months and minimum of five patients for analysis. Exclusion criteria for our review were all non-English language studies, papers that exclude single or two-stage exchange, review papers, case reports or technique articles without outcome data. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were applied. Title and abstract screen was conducted of 248 results and a full text review of 66, identified 31 articles that met inclusion and exclusion criteria for final review.

The purpose for this review was to understand and compare the role of single-stage and two-stage exchange for the treatment of shoulder PJI. Two-stage exchange arthroplasty with implant removal, irrigation and debridement (I&D), insertion of antibiotic spacer, antibiotic treatment, followed by re-implantation has been suggested as gold standard for treatment of shoulder PJI [1]. Varying studies collected demographics, timing of infection, associated pathogens, surgical treatment, antibiotics, eradication rate for infection, surgical complications and functional outcomes with two-year follow-up minimum. We identified 12 articles that evaluated one-stage exchange and 27 articles that evaluated two-stage exchange. The majority of papers reported preoperative laboratory values to diagnose PJI based on elevated white blood cell count, C-reactive protein and/or erythrocyte sedimentation rate. Clinical findings such as draining sinus, erythema or swelling were inconsistently reported. Most studies reported the number of joint aspirations performed and resulted positive with microbial growth. Although there was inconsistent reporting of timing of infection, the majority of studies that reported timing of infection used terms from Sperling et al. and Strickland et al. with acute meaning < 3 months, sub-acute meaning 3-12 months and chronic > 12 months [2,3]. There was consistent reporting of the pathogens found either pre- or intraoperatively. *Cutibacterium acnes* (*C. acnes*) was the most common organism identified with 160 cases followed by *Coagulase-negative Staphylococcus* (CoNS) with 93 cases [2,4–14]. There were 57 reported cases of polymicrobial cases and 27 cultures that resulted in no growth [4–8].

To address the stated question, we reviewed studies in aggregate for sub-acute and chronic infection when treated with either single

TABLE 1. Reinfection and complications for single stage exchange

Cases	Reinfection Rate	Pathogens	Constant Score (mean)	Complication Rate
161 Total 13 Subacute 8 Chronic	5.6 % ($p < 0.001$)	72 *C. acnes* 29 CoNS 20 MSSA 3 MRSA	49.1 ($p < 0.11$)	12.7 % ($p < 0.001$)

CoNS, Coagulase-negative *Staphylococcus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*

TABLE 2. Reinfection and complications for two-stage exchange

Cases	Reinfection Rate	Pathogens	Constant Score (mean)	Complication Rate
325 Total 46 Subacute 74 Chronic	11.4 % ($p < 0.001$)	88 *C. acnes* 64 CoNS 33 MSSA 56 MRSA	51.1 ($p < 0.05$)	21.9 % ($p < 0.001$)

CoNS, Coagulase-negative *Staphylococcus*; MSSA, methicillin-susceptible *Staphylococcus aureus*; MRSA, methicillin-resistant *Staphylococcus aureus*

or two-stage revision summarized in Tables 1 and 2. Four studies directly compared revision success rate for shoulder PJI with single-stage exchange in sub-acute or chronic presentation. The reinfection rate was 12.5% for chronic cases and 5.3% for sub-acute cases [4,14,15]. Regarding two-stage exchange, three studies specifically reported success rates for either sub-acute or chronic shoulder PJI. Reinfection rate was 6.3% for chronic PJI and 29.4% for sub-acute PJI treated with two-stage exchange [2,4,15]. Several other studies reported the timing of infection but did not compare revision failure rates according to the subgroups of acute, sub-acute or chronic PJI groups. In aggregate, using a frequency-weighted mean, the reinfection rate was 5.6% for one-stage exchange compared to 11.4% for two-stage exchange, which was statistically significant ($p < 0.001$).

Analyses of complications related to single or two-stage exchange in acute, sub-acute or chronic infection were limited. In aggregate, all surgical complications reported include aseptic loosening, fracture, nerve palsy, dislocation and hematoma. Our systematic review found a 12.7% complication rate for single-stage exchange compared to a 21.9% complication rate for two-stage exchange, which was statistically significant. Although this finding suggests that patients undergoing two-stage exchange have 1.72 times the risk of intra- or postoperative complication, the analysis was not able to account for likely bias in the selection of treatment. The selection bias cannot be over-emphasized—it very well may be that cases with more severe infections were preferentially treated with two stage while less severe infections were treated with single-stage revision.

Frequency-weighted mean Constant Murley Score (CMS) was 49.1 for single-stage patients and 51.1 for two-stage exchange, which was similar to prior findings [7,15]. In the single-stage studies, a total of 57 patients had 78.2 degrees of FF; 42 patients had 52.4 degrees of abduction and 59 patients had 25.4 degrees of external rotation. Two-stage exchange papers reported 194 patients had 98.9 degrees of FF, 72 patients with 52.4 degrees of abduction and 144 patients with 29.2 degrees of external rotation. No studies compare the timing of infection and treatment with single or two-stage revision.

All papers identified are retrospective thus contain significant selection bias. While our findings in aggregate suggest single-stage exchange is a viable option for PJI, there are few studies that address reinfection associated with various risk factors such as pathogens, timing of infection or diagnostic features such as obvious clinical findings of infection. Thus, we cannot recommend using single-stage exchange in place of two-stage exchange for shoulder PJI without further investigation.

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QUESTION 4: Is there a role for preoperative joint aspiration prior to reimplantation during two-stage exchange for shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: There is a dearth of information on the role of preoperative joint aspiration prior to second stage revision after treatment of shoulder PJI. Furthermore, several studies have pointed to the high incidence of "dry taps" and false negative cultures from joint aspirates. Thus, there is little evidence in support of routine preoperative aspiration prior to second stage reimplantation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 88%, Disagree: 4%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

A systematic review of the published literature was performed on PubMed using the search terms Shoulder (Title) AND [Periprosthetic OR reverse shoulder OR total shoulder OR arthroplasty OR replacement OR prosthesis (Title/ Abstract)] AND [Infection OR infected OR septic OR sepsis OR PJI OR propionibacterium OR acnes OR staphylococcal OR staphylococcus OR second stage OR OR staged OR revision OR spacer OR two-stage OR two stage OR reimplantation OR purulent OR purulence OR sinus tract (Title)]. This search yielded 255 articles. All titles were reviewed and articles with potential relevance had their abstracts reviewed. In total, with full texts reviewed, 31 articles where considered relevant to this topic in some fashion. Articles were deemed relevant if they included any aspirate information on patients with shoulder arthroplasties. These articles were used to make the recommendation. The reference lists of the included articles were further searched to identify other references that may have been omitted.

Controversy remains regarding the best surgical treatment of shoulder PJI. The literature documents interventions including open debridement with component retention or liner exchange, single stage re-implantation comprising removal of all components and immediate re-implantation after thorough debridement and lavage, resection arthroplasty after removal of all components and two-stage re-implantation. The latter involves a first stage that includes removal of all components followed by debridement, and in many cases insertion of an antibiotic impregnated polymethylmethacrylate cement spacer for local antibiotic delivery and to preserve soft tissue tension. The patient is then treated with intravenous (sometimes followed by oral) antibiotics and monitored, typically with serial serologic evaluation, prior to the second surgery (second stage revision) at which time the spacer is removed and new components are re-implanted.

In patients who undergo two-stage re-implantation for shoulder PJI, shoulder joint aspiration or arthrocentesis prior to second stage revision is one method to evaluate for persistent infection after the first stage explantation and subsequent antibiotic treatment. The aspirate can be sent for cultures, leukocyte cell count and differential, and also for analysis of biomarkers such as alpha-defensin. Shoulder aspiration is an established diagnostic tool and is commonly used (although not routinely) as part of the workup of PJI, including shoulder PJI.

However, there is little published information on the use of shoulder aspiration prior to second stage revision. In addition, there is no data documenting an advantage of shoulder aspiration over no aspiration or over any alternative diagnostic tool for shoulder PJI. Sabesan et al. reported that 12 of 17 patients had preoperative aspiration prior to the first stage. re-implantation [1]. Fluid was obtained for culture in 10 and 6 had positive cultures. Prior to the second stage the patients were ruled out for persistent infection with preoperative erythrocyte sedimentation rate, C-reactive protein (CRP), white blood cell (WBC) count and a negative preoperative aspirate. One of the 17 patients had intraoperative frozen section that was positive for acute inflammation and had repeat treatment for infection. Two small case series studies recommend preoperative aspiration prior to considering second stage revision, but only in cases with persistently elevated CRP and WBC [2,3]. Buchalter et al. have described their algorithm for two-stage re-implantation for shoulder PJI but do not mention shoulder aspiration as a factor in their timing of second-stage revision [4]. Patients were offered a second stage reimplantation if they had no clinical signs of infection and their inflammatory markers normalized.

If shoulder joint aspiration is considered in the evaluation for PJI, it is typically recommended to hold antibiotics for at least 14 days prior to aspiration [2,3,5]. It is also important to note that a negative culture of fluid aspirate or dry aspirate is not diagnostic of a resolved infection based on studies that include preoperative shoulder aspirations [5,6].

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Authors: Gregory Cvetanovich, Anthony Romeo

QUESTION 5: Is there a role for pre-reimplantation open or arthroscopic tissue biopsy in the evaluation during two-stage exchange of shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: Unknown. There is one level IV study suggesting that open biopsy prior to second-stage revision for shoulder PJI can identify patients with persistent infection who may benefit from subsequent repeat irrigation and debridement (I&D) prior to second stage reimplantation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

PubMed and Embase were searched from 1980 to January 2018 to identify studies evaluating preoperative open or arthroscopic tissue biopsy prior to second stage revision shoulder arthroplasty after treatment of shoulder PJI. A secondary search of the references of included studies was also conducted. One article was selected for inclusion. Articles regarding hip and knee arthroplasty were excluded.

Zhang et al. reported a level IV case series in which they performed open biopsy prior to second stage revision for treatment of shoulder PJI [1]. Eighteen patients with shoulder PJI between 2005 and 2012 were included. Patients were treated with a standard protocol involving I&D, removal of implants, antibiotic spacer placement and antibiotic therapy based on culture results for six weeks based on infectious disease service recommendations. At a minimum four weeks after completion of antibiotics, patients were re-evaluated to ensure no clinical symptoms of infection were present and erythrocyte sedimentation rate/ C-reactive protein (ESR/CRP) had normalized. At this point, all patients underwent open biopsy via deltopectoral incision to obtain at least three soft tissue and bone cultures from tissue adjacent to the bone-antibiotic spacer interface. If cultures were negative for 7 to 14 days, patients underwent reimplantation. If cultures were positive, patients instead underwent repeat I&D with antibiotic spacer exchange and the protocol was repeated.

Zhang et al. found that 4 of 18 patients (22%) had positive cultures from the open biopsy indicative of persistent infection with a 38% persistent infection rate for individuals infected with *C. acnes*. One patient had positive cultures again on second open biopsy and underwent a second spacer exchange prior to finally obtaining a negative third biopsy and undergoing reimplantation. *C. acnes* was the most common pathogen, present in 44% of index shoulder PJIs. Among persistent infections, 3 of 4 patients (75%) had *C. acnes*, and the patient requiring two spacer exchanges had *C. acnes* on each occasion. At a mean of 24 month follow-up (range 12 to 36 months), all 18 patients were reimplanted (2 hemiarthroplasty, 1 total shoulder arthroplasty (TSA), 15 reverse total shoulder arthroplasty (RTSA)) and noted to be clinically infection-free with an average American Shoulder and Elbow Surgeons (ASES) score of 71.

This study is limited in its level IV design and small sample size. Furthermore, patients undergoing two-stage revision had variable index procedures from which they developed shoulder PJI, including one open reduction internal fixation (ORIF) proximal humerus fracture, three hemiarthroplasties, six rotator cuff repairs, five TSAs and three RTSAs. There is no comparison group of patients who did not undergo open biopsy, and no comparison to alternative methods such as shoulder aspiration or arthroscopic biopsy.

The role of open or arthroscopic biopsy prior to reimplantation during a two-stage exchange arthroplasty remains unclear.

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PART IV

SPINE

Prevention

1.1. PREVENTION: GENERAL PRINCIPLES

Authors: Steven Schmitt, Christopher Kepler

QUESTION 1: What can one do if an inadvertent contamination during instrumented spine surgery occurs?

RECOMMENDATION: There is no data to support a particular strategy in preventing infection after inadvertent contamination of spinal implants.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Left uncovered in the operating suite, spinal implants can become contaminated within 30 minutes [1]. There are no human data to support a particular algorithm for management of inadvertent contamination. In animal studies, tobramycin powder has been shown to reduce infection in contaminated spine surgery and vancomycin powder has been shown to reduce infection in contaminated knee surgery [2,3]. At least one suggests that management of inadvertent contamination should be individualized to the clinical situation and stage of surgery, and many surgeons are reluctant to proceed with implant surgery if contamination has occurred. Some experts recommend intraoperative irrigation with solutions containing antibiotics, without supporting data (personal communication).

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Author: Maja Babic

QUESTION 2: How should spine surgery patients with postoperative diarrhea be managed?

RECOMMENDATION: Diarrhea can be managed in a standard approach with careful attention to the surgical site.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 93%, Disagree: 0%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Postoperative diarrhea poses a risk of contaminating the surgical incision. Maintaining a clean and dry surgical site is crucial. Postoperative diarrhea is generally self-limiting but infectious etiologies, especially *C. difficile*, are particularly concerning in the inpatient setting and should be ruled out. After infectious causes are ruled out, a standard approach should be implemented to address diarrhea including discontinuing potentially inciting medication (antibiotics), increasing fiber content and using antisecretory (i.e., bismuth subsalicylate) and antimotility (i.e., loperamide) agents. A balanced electrolyte rehydration should also be utilized. The use of probiotics and prebiotics can be used in cases of post-antibiotic-associated illness [1].

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1.2. PREVENTION: ANTIMICROBIALS

Authors: Alexander Montgomery, Rajesh Mangattil

QUESTION 1: Is there a role for oral antibiotics in the prevention of infection in patients with draining wounds following spinal surgery?

RECOMMENDATION: There is no reliable evidence for the use of prophylactic oral antibiotic therapy in patients with draining wounds after spine surgery.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 93%, Disagree: 7%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

The incidence of spinal surgical site infection (SSI) has been reported to be from 0.7–16% [1–3]. Surgical drains are used in spine surgery to avoid the risk of a hematoma formation leading to potential neurological deficit [4]. Drains retained for a longer period have been shown to have a higher rate of bacterial contamination [5]. However, not using a drain has been found to be associated with the development of late-onset SSI [6,7]. Therefore, the use of drains decreases wound drainage and consequently decreases infection rates [8,9]. Prophylactic antibiotic cover for 24 hours has now become a standard of care following orthopaedic procedures [10].

Since the first systematic review on prophylactic measures against spinal SSI was published by Brown et al. in 2004 [11], there has been a considerable increase in the preventive strategies documented in the spine literature. However, many studies are of lower methodological quality with significant heterogeneity [12].

There was only one prospective randomized study showing no significant difference in the infection rates between patients receiving prophylactic antibiotic coverage for 24 hours or for the entire duration that the drain was in place. This study was on thoracolumbar fractures. It was not clear if the antibiotic cover was administered orally or parenterally [13]. In a review of 560 cases of closed suction drainage in single level lumbar decompressions, Kanayama et al. did not report on the use of prophylactic oral antibiotics [14]. Similarly, a 2018 systematic review by Yao et al. identified 11 randomized controlled trials (RCTs), 51 case-controlled studies (CCS) and 77 case series. They reported wide variations in the surgical indications, approaches and definitions of SSI. They found strong evidence that closed-suction drainage does not affect SSI rates, but had no mention of the use of prophylactic oral antibiotic therapy [15].

There were many studies that evaluated the risk factors for wound complications following spine surgery [16–18]. Past studies are archaic in nature with very little contribution or relevance to these authors. A staged treatment algorithm for spine infections did not specify or address the indication for oral antibiotics to prevent infection in draining wounds [19]. A recent retrospective study attributed the drain volume and time to the risk factors for SSI after lumbar surgery. There was no direct reference to the impact of oral or parenteral antibiotics in their study [13,20].

A systematic evidenced-based review included 36 observational studies involving 2,439 patients. However, these were non-interventional studies to evaluate the independent risk factors for patients developing SSIs following spine surgery [17]. In their systematic review and meta-analysis of wound drains in non-instrumented lumbar decompression surgery, Davidoff et al. included 5,327 cases who received drains. They found that the SSI rates were unaffected by the routine use of drains. However, none of these patients had prophylactic oral antibiotics [21]. Ho et al. reported a retrospective review of 70 patients who had undergone single-level lumbar discectomy. They suggested that surgical drains do not increase SSI risk and that drain tip cultures allow detection of postoperative infection at a very early stage. They found that this would lead to quicker initiation of antibiotic treatment [22].

Apart from a prospective randomized study that suggested no difference in the infection rates, there are no studies directly linking the role of oral antibiotics in the prevention of infection in patients with draining wounds following spine surgery [13]. Therefore, in the absence of reliable evidence, only a consensus recommendation can be made based on clinical opinion.

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QUESTION 2: Is there a role for the addition of gentamicin to perioperative prophylactic antibiotics in spine surgery?

RECOMMENDATION: No, we recommend AGAINST the inclusion of gentamicin for perioperative prophylaxis in spine surgery. There is no data suggesting that the addition of gentamicin to systemic perioperative prophylactic antibiotic regimens decreases the rate of postoperative infections, and strong evidence showed that it is associated with harm (namely nephrotoxicity). The question of the use of local/topical gentamicin is unresolved.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 62%, Disagree: 15%, Abstain: 23% (Super Majority, Weak Consensus)

RATIONALE

The use of gentamicin to expand the gram-negative activity for perioperative antimicrobial prophylaxis in spine surgery has been considered for decades, yet positive outcomes data for this practice are lacking. Pons et al. reported on a randomized, blinded study of 826 patients undergoing neurosurgical procedures, including spine surgery, and found similar surgical site infection (SSI) rates for those assigned to ceftizoxime or vancomycin and gentamicin [1]. Ramo et al. reported on a multivariate analysis of 428 posterior spinal fusion patients and found that the addition of an aminoglycoside did not lower the SSI rate [2]. In a mixed population of more than 11,000 orthopaedic surgery patients treated over 5 years in the United Kingdom, Walker et al. noted no difference in SSI rates during a period when a combination of flucloxacillin and gentamicin was given for prophylaxis compared to one where co-amoxiclav was the prophylactic regimen of choice [3].

The association of aminoglycoside prophylaxis (even single-dose) for orthopaedic surgery and acute kidney injury (AKI) has now been well-documented. Dubrovskaya et al. reviewed more than 4,000 patients undergoing orthopaedic surgery, comparing those receiving a single dose of gentamicin combined with another antibiotic to those receiving non-aminoglycoside prophylaxis alone. Although for all patients the addition of gentamicin was not associated with AKI, gentamicin was associated with a statistically significantly higher rate of AKI for those undergoing spine surgery [4]. Bell et al. reported on a Scottish initiative where routine surgical prophylaxis was changed from cefuroxime to flucloxacillin and gentamicin (single-dose) between 2006 and 2010. Among 7,666 patients undergoing orthopaedic surgery, the gentamicin-containing regimen was associated with a 94% higher incidence of AKI [5]. Finally, in the previously-cited study by Walker et al., a change from routine prophylaxis with flucloxacillin and gentamicin to co-amoxiclav alone was associated with a 63% reduction in postoperative AKI [3].

Two meta-analyses on the association of gentamicin prophylaxis with nephrotoxicity have been published. Luo et al. compared the use of gentamicin and flucloxacillin to cefuroxime alone in studies of diverse surgery types. The risk of postoperative renal impairment was higher in the gentamicin group, especially for those undergoing orthopaedic surgery [6]. Srisung et al. analyzed 11 studies containing 18,354 patients comparing gentamicin versus non-gentamicin surgical prophylaxis regimens. Using random effects modeling, gentamicin prophylaxis in orthopaedic surgery was associated with a significantly higher risk of AKI (risk rate (RR) 2.99; 95% confidence interval (CI): 1.84, 4.88) [7].

Data regarding the use of topical or local wound gentamicin are limited. In a single-center study, van Herwijnen et al. reported a higher SSI rate for patients undergoing scoliosis surgery who received wound irrigation with gentamicin versus povidone-iodine [8]. On the other hand, Borkhuu et al. reported on 220 children undergoing spinal fusion and found a four-fold reduction in SSI for those treated with gentamicin-impregnated bone allograft [9]. Han et al. retrospectively analyzed data from 399 patients undergoing spine surgery. Among patients who had a gentamicin-impregnated collagen sponge applied to their wound, the SSI rate was 0.8%, versus 5% for those treated without the sponge [10]. At this time, however, given the variability in reported application methods for local gentamicin and the small number of patients studied, the routine use of topical gentamicin cannot be recommended.

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QUESTION 3: Should prophylactic antibiotic prophylaxis be repeated during spine surgery? If so, when?

RECOMMENDATION: In most uncomplicated spinal procedures, a single preoperative dose of prophylactic antibiotics is sufficient. Prophylactic antibiotics should be redosed intraoperatively for procedures lasting longer than twice the half-life of the antibiotic, or if there is excessive blood loss (blood loss > 1,500 mL) in order to ensure therapeutic levels.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 0%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

There are no randomized spine studies that compare the effectiveness of redosing prophylactic antibiotics during surgery to preoperative antibiotics alone. Therefore, this review was expanded to include other surgical subspecialties. Several major guidelines including those from the North American Spine Society (NASS), Infectious Disease Society of America (IDSA) and Surgical Infection Society (SIS) have made similar recommendations supported by pharmacokinetic data and retrospective studies [1,2]. Furthermore, the Centers for Disease Control and Prevention (CDC) recently noted that there is insufficient-quality evidence to make a recommendation regarding whether or not antibiotics should be redosed intraoperatively [3].

In a prospective study of 57 subjects undergoing elective surgery, an analysis of intraoperative serum cefazolin concentrations at approximately 3.5 hours after receiving a preoperative dose showed that antibiotic concentrations dropped below the minimum inhibitory concentration (MIC) for methicillin-susceptible *Staphylococcus aureus* (MSSA) and *Escherichia Coli* (*E. Coli*) [4]. Ohge and colleagues found that cefazolin concentrations had dropped below 80% of the MIC in the adipose tissue and peritoneum for multiple bacteria three hours after the preoperative dose was administered [5]. In a prospective study of 11 elective instrumented spinal procedures with a large expected blood loss, estimated blood loss (EBL) was found to have a strong negative correlation with cefazolin tissue concentrations ($r = -0.66$, $p = 0.5$). Based on the pharmacokinetic values, the authors recommended that procedures with an EBL greater than 1,500 mL should receive an additional dose of cefazolin [6].

In a retrospective study of 1,548 patients undergoing cardiac surgery, intraoperative redosing for procedures lasting greater than 400 minutes was shown to reduce the risk of surgical site infections (SSIs) (adjusted OR 0.44, 95% CI 0.23-0.86) [7]. Similarly, Scher et al. demonstrated that for surgeries longer than three hours, patients who were redosed with cefazolin intraoperatively had a lower SSI rate than those who only received preoperative cefazolin (6.1% vs. 1.3%, $p < 0.01$) [8]. In another retrospective review of 4,078 patients undergoing various general surgery procedures, cases with an EBL of greater than 500 mL or those that were not re-dosed intraoperatively during longer cases were associated with a higher rate of SSI [9].

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QUESTION 4: Should vancomycin powder be applied to the wound in patients undergoing spinal surgeries? Are there any potential harms associated with this practice?

RECOMMENDATION: Yes. Evidence suggests that vancomycin powder applied to the wound during spinal surgery reduces the risk of infection. However, the majority of studies lack a control arm and it is not known if vancomycin powder is better than antiseptic agents. There is insufficient evidence for or against the potential harm associated with this practice.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 79%, Disagree: 14%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Surgical site infection is a known risk of spine surgery with or without instrumentation, and gram-positive organisms are the most common pathogens in such infections. Many practitioners now apply vancomycin powder intraoperatively to reduce the risk of infection. Given concern for vancomycin's adverse effects and antimicrobial resistance, it is critical to consider a risk-benefit analysis of this practice.

A number of studies addressed the efficacy of vancomycin powder use in spine surgery. These have been the subject of several systematic reviews. Xie et al. reviewed 19 retrospective cohort studies and 1 prospective case study, with results suggesting benefit in all but 2 of these with an overall infection risk of 2.83-fold higher for patients not receiving vancomycin powder compared to those receiving it [1]. The authors pointed out study heterogeneity with regard to powder, drug dosage and exposure of bone graft and instrumentation to the drug, citing these as areas for future investigation. This trend toward benefit was confirmed in five other systematic reviews [2–6].

With regard to adverse effects, Ghobrial et al. performed a systematic review of 16 studies with 6,701 patients [7]. Of these, 1 patient developed nephropathy, 2 patients experienced hearing loss, 1 patient had an elevated vancomycin level and 19 patients developed culture-negative seroma. The authors highlighted the lack of in vivo evidence regarding vancomycin resistance. There was a trend toward gram-negative and polymicrobial infections among vancomycin powder recipients in one study [8].

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QUESTION 5: What is the optimal perioperative antibiotic prophylaxis for patients undergoing spine surgery? What considerations should be made in cases of drug allergies?

RECOMMENDATION: The optimal prophylactic antibiotic for an uncomplicated spine surgery is a first- or second-generation cephalosporin given intravenously within 60 minutes of initial incision.

In patients with a history of anaphylactic reaction after use of beta lactams or in countries with a high rate of methicillin-resistant *Staphylococcal* infections, vancomycin in a weight-adjusted dose (15 mg/kg) should be used. Clindamycin 600 mg intravenously is an alternative to vancomycin.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 79%, Disagree: 7%, Abstain: 14% (Super Majority, Strong Consensus)

RATIONALE

Current literature supports the use of prophylactic antibiotics for spinal procedures with or without instrumentation to decrease the risk of surgical site infections (SSI), with a first- or second-generation cephalosporin being the antibiotic of choice [1–6]. In addition, clin-

ical guidelines set forth by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS), the Society for Healthcare Epidemiology of America (SHEA) and the North American Spine Society support the use of first-generation cephalosporins [1,7,8]. Although comparative studies to evaluate the optimal timing for preoperative antibiotic have not been conducted for spine surgery, it is well-established that intravenous cephalosporins given within 60 minutes before initial incision is effective [9,10].

In a comparative study evaluating the addition of vancomycin powder for posterior thoracic and lumbar spine surgery, Sweet et al. found that vancomycin powder reduced the rate of SSI compared to intravenous cephalexin alone (0.2% vs. 2.6%, $p < 0.0001$).

Regarding prophylaxis regiments combining antibiotic agents, randomized clinical trials exist which show a reduced rate of postsurgical infections if a combination of a cephalosporin and gentamicin or vancomycin and gentamicin is used, compared to placebo [11,12]. However, there are no studies available which compare combination regimens with the standard prophylaxis with cefazolin. A study by Pons et al. comparing ceftizoxime versus the combination prophylaxis with vancomycin and gentamicin found no decreased infection rate, but higher toxicity with the combination regimen [13].

There is no specific recommendation for adapted prophylaxis in obese patients in spine surgery. However, in periprosthetic joint infections, adaptation is discussed in patients with a weight more than 100 kg since infection rate was twice that in other patients [13–15].

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QUESTION 6: What are the optimal prophylactic antibiotics for patients with neurogenic bladder who are undergoing spine surgery?

RECOMMENDATION: The recommended standard perioperative antibiotic prophylaxis in spine surgery is cefazolin, but a broader-spectrum prophylaxis may be necessary in patient subpopulations more prone to acquiring surgical site infections (SSIs). In the case of neurogenic bladder, preoperative urine culture and individualized antibiotic prophylaxis are associated with a significant decrease in SSIs due to gram-negative bacilli (GNB).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 79%, Disagree: 14%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Prevention of SSI is of utmost importance in patients undergoing spine surgery, and perioperative antibiotic prophylaxis is a key measure to avoid this complication [1,2]. However, the superiority of one agent or schedule over any other has not been clearly demonstrated [1,2]. The recommended standard perioperative antibiotic prophylaxis in spinal surgery is cefazolin [1]. Isolated reports have shown that a broader-spectrum prophylaxis may be necessary in patient subpopulations more prone to acquiring poly-microbial SSI, such as those with neuromuscular deformities or spinal cord injury. In a retrospective observation study, Dessy et al. demonstrated that an enhanced antibiotic prophylaxis using intravenous (IV) cefuroxime for 24 hours plus vancomycin until drain removal in instrumented spinal surgery, and IV cefuroxime for 24 hours in non-instrumentation cases reduced the rate of SSIs in spine surgery [3].

There are no published data regarding the best antibiotic treatment to be used as prophylaxis in patients with neurogenic bladder. The North American Spine Society (NASS) evidence-based guidelines on antibiotic prophylaxis in spinal surgery have pointed out that potential subgroups of patients requiring effective prophylaxis against GNB may exist, although they have not been clearly defined [1]. In the case of patients with neurogenic bladder, they are more prone to urinary tract colorization and infection [4–5]. Although

asymptomatic bacteriuria (AB) should not be routinely treated in these patients because of rising resistance patterns, in the case of symptomatic urinary tract infection (UTI) antibiotic treatment should be administered and antibiotic selection should be based on local and patient-based resistance patterns so that the spectrum can be as narrow as possible [5]. In this line, recent Clinical Guidelines for the Diagnosis and Treatment of UTI of the Spanish Society of Infectious Diseases state that screening for, and treatment of, AB prior to performing instrumental spinal surgery is recommended for patients with neurogenic bladders or urinary incontinence in order to reduce the risk of gram-negative SSIs [6].

It was reported that up to 61% of children with myelomeningocele have neurogenic bladders [7–9]. Hatlen et al. demonstrated that the presence of positive urinary cultures before elective spine surgery for children with myelomeningocele leads to an increased risk of perioperative spine infections [10]. Olsen et al. conducted a case-control study to determine independent risk factors for SSI following orthopaedic spinal operations [11]. Among the patient-level factors in the univariate analysis, any incontinence (bowel or bladder, or both and preoperative or postoperative) significantly increased the risk of SSIs.

Although gram-positive organisms (particularly *Staphylococcus aureus*) predominate as causative agents for SSIs in patients undergoing spine surgery, GNB accounted for a sizeable portion of SSIs, particularly among lower lumbar and sacral spine surgical procedures [2]. Patients with incontinence, neurogenic bladder or indwelling catheters are more prone to urinary tract colonization and infection and may therefore be at higher risk of SSIs by GNB [4]. Contamination by GNB should not occur during the operative procedure, as these microorganisms are not usually present among the patient's skin flora [12]. Previous studies have suggested that GNB contamination could be secondary to hematogenous seeding originating in the urinary tract or to local skin contamination in incontinent patients, especially those undergoing surgery at the lumbosacral level [12].

Nuñez-Pereira et al. hypothesized that detecting urinary tract colonization preoperatively and adjusting antibiotic prophylaxis according to urine culture results might lower the overall SSI rate by reducing the number of GNB infections [12]. They performed a retrospective cohort study comparing two consecutive groups of patients undergoing posterior spinal fusion and instrumentation at a single institution. Cohort A included 236 patients, operated on between January 2006 and March 2007, receiving standard preoperative antibiotic prophylaxis with cefazolin (clindamycin in allergic patients). Cohort B included 223 patients operated on between January and December 2009, receiving individualized antibiotic prophylaxis and treatment based on preoperative urine culture. The study demonstrated that preoperative urine culture and individualized antibiotic prophylaxis are associated with a significant decrease in SSI due to GNB in high-risk patients undergoing spinal surgery.

Measures aimed at preventing UTI in patients with neurogenic bladder such as closed catheter drainage in patients with an indwelling catheter and the use of clean intermittent catheterization could reduce the risk of perioperative spine infections [4]. Intravesical Botox, bacterial interference and sacral neuromodulation show significant promise for the prevention of UTIs in neurogenic bladder patients [5].

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1.3. PREVENTION: BONE GRAFT

Author: Dolors Rodriguez-Pardo

QUESTION 1: Does the use of allograft increase the risk of spinal infection?

RECOMMENDATION: The use of allograft seems to increase the risk for infection in pediatric and neuromuscular scoliosis, however there is no increased risk in the adult degenerative population.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 77%, Disagree 0%, Abstain: 23% (Super Majority, Strong Consensus)

RATIONALE

It has been postulated that infection risk from bone allograft may be caused by contamination or by the overwhelming of local host defenses [1,2]. Much of the data addressing this issue can be found in the pediatric literature. In a case-control study of 22 pediatric patients with infections after spine surgery, Croft et al. found that allograft use was strongly associated with surgical site infection (odds ratio (OR) = 10.7, $p < 0.0001$) [3]. Aleissa et al. showed similar results in 14 patients with SSI (risk rate (RR) 9.6, $p < 0.001$) [4]. Sponseller et al. were able to demonstrate a statistically significant increase in infection risk with the use of allograft versus autograft ($p = 0.010$) [5].

Several systematic reviews have also addressed this subject. Fei et al. performed a meta-analysis of risk factors for surgical site infection after spine surgery in 12 high-quality studies [6]. They found a relative risk for infection of 2.72% with the use of bone allograft, though there was a broad confidence interval and they failed to reach statistical significance at $p = 0.244$. Meng et al. [2] performed a systematic review of 13 studies of infection risk in pediatric spine surgery. The use of allograft carried an odds ratio of 8.498 with a high statistical significance at $p < 0.001$, though the authors cautioned about possible bias due to study heterogeneity. Glotzbecker et al. found grade C evidence of an association between allograft use and surgical site infection [7].

On the other hand, multiple studies have demonstrated that even in the pediatric literature, there is conflicting evidence. Knapp et al. studied patients with Adolescent Idiopathic Scoliosis (AIS) and found that allograft did not increase the risk for infection [8]. In a case-control study of pediatric patients undergoing spinal fusion, Shen et al. also found that there was no increased risk with allograft [9]. In the adult population, several large studies have failed to find an association between allograft use and infection. Mark et al. looked at over 1,400 patients who underwent spinal fusion, and there was no difference in infection rate when using allograft or autograft [10]. Similarly, Saeedinia et al. looked at almost 1,000 patients undergoing spinal surgery and failed to find an association between allograft and infection [11].

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Authors: Steven Schmitt, Christopher Kepler, Wesley Bronson

QUESTION 2: Can allograft, synthetic bone substitute or autograft be used during revision spinal surgery in patients with prior spine infection?

RECOMMENDATION: Based on available data, it appears that allograft, autograft and synthetic cages may be used successfully along with posterior screw fixation and prolonged antibiotic therapy in the treatment of pyogenic spondylodiscitis. This data can probably be extrapolated to also confirm that allograft and autograft safe during revision spinal surgery with prior infection.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 7%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

There are several small studies suggesting that bone allograft and autograft may be used successfully with posterior screw fixation and antibiotics to treat spine infections. Dobran et al. reviewed 18 patients who underwent posterior screw fixation along with allograft and autograft for pyogenic spondylodiscitis [1]. All patients had successful fusion and normalization of C-reactive protein at a mean follow-up of 30 months. Likewise, Chung et al. reported a study of 20 patients who underwent anterior fibular allograft and posterior screw fixation for spondylodiscitis [2]. All patients had significant improvement in pain and satisfaction scores, with at least 36 months of follow-up. Only two patients had superficial wound complications. In a third study, An et al. reviewed 15 patients who underwent mixed allograft and autograft with posterior screw fusion [3]. All but one showed significant improvement in neurological deficit, functional outcome and pain, with a mean follow-up of 27 months.

Synthetic materials have also been used in the successful treatment of pyogenic spondylodiscitis. Shiban et al. reported 52 patients treated with polyetheretherketone (PEEK) cages in combination with posterior pedicle screw fixation [4]. Patients received two weeks of intravenous and three months of oral antibiotic therapy. Infection was cured in all and 16 of the 28 with some neurologic deficit improved at 12 months of follow-up. Similar results were reported with PEEK cages and posterior fixation by Schomacher et al. (51 patients, 20 months of follow-up) and Brase et al. (nine patients,

mean follow-up 13 months) [5,6]. One study compared three different types of cages (titanium mesh, titanium and PEEK) versus autologous iliac bone strut [7]. All received posterior screw fixation. There were no significant differences in clinical or radiographic outcomes, and infections were judged cured in all at a mean of 36 months for follow-up. Multiple other studies report similar findings [8–10].

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1.4. PREVENTION: RISK FACTORS

Authors: Koji Yamada, Yoshihirio Uchida

QUESTION 1: Does prior or active tuberculosis (TB) preclude patients from undergoing spine surgery?

RECOMMENDATION: Prior or active TB does not preclude patients from undergoing spine surgery.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The mainstay of treating spinal TB is chemotherapy [1]. Almost all antituberculous drugs penetrate well into tuberculous lesions [2], more than the desired minimum inhibitory concentrations (MIC) [3,4]. Abscesses usually resolve with medical therapy, as antituberculosis drugs penetrate very well [5,6].

There is controversy in the literature about the necessity of using surgical intervention in addition to spinal TB treatments. A Cochrane Database Review assessing the role of routine surgery in addition to chemotherapy in spinal TB including the studies from Medical Research Council (MRC) of the United Kingdom failed to reveal any statistically significant differences in various outcomes for additional surgery including: kyphosis angle, neurological deficit (none went on to develop this), bony fusion, absence of spinal TB, death from any cause, activity level regained, change of allocated treatment or bone loss [1]. Myelopathy with or without functional impairment most often responds to chemotherapy [7]. In two MRC studies conducted in Korea, more than 80% of patients had complete resolution of myelopathy or complete functional recovery when treated medically [8,9].

Though the review of the above trials was insufficient to say routine surgery early on was beneficial, several limitations exist [1]. First, two sets of trials reviewed in the literature were performed during the 1960s and 1970s, while in recent years new medications and better operative techniques have been developed. Second, the patients included in the MRC study were limited to two-vertebra disease with or without mild neural deficit [10,11]. The results for patients with moderate to severe motor weakness were not addressed. Moreover, the patients seen in developing countries often have a large number of vertebrae involved, accompanied with a greater chance of kyphosis progression [12] and late onset paraplegia [13,14]. Third, late onset paraplegia usually become present more than 15 years after initial spinal infection [15–17]. In MRC studies, increased progression of kyphosis was seen in the conservatively-treated group with a lower fusion rate during their follow-up period [18]. Considering the difficulties in treating severe late symptomatic post TB kyphosis, the follow-up period in these studies could be insufficient to detect the magnitude of late complications. Fourth, it is generally known that some patients do not respond well to conservative treatment and are considered nonresponders [19]. For these patients, surgery should be considered to procure adequate tissue to ascertain the diagnosis as well as to reduce the disease load.

Potential benefits of surgery include less kyphosis, immediate relief of compressed neural tissue, quicker relief of pain, a higher percentage of bony fusion, quicker bony fusion, less chance of relapse, earlier return to previous activities and less bone loss [1,2]. Early surgical intervention for prevention of deformity is relatively simple and may prevent late neurological problems due to kyphosis of the spine [15,20,21]. From a review of 124 articles, 17.1% of the procedures were performed with defined indications including: etiology, neurological deficit (severe or progressive), spinal instability with or without kyphosis (severe or progressive), multisegmental disease and paraplegia of greater than three months [19]. Surgical interven-

tion for those without neurological recovery/improvement after chemotherapy for moderate motor weakness and surgical decompression of the cord under the cover of multi-drug chemotherapy for severe motor weakness irrespective to the duration of illness or cause, are also recommended [22].

Medical treatment is generally effective for those with or without mild neural deficit. Surgical intervention may be indicated in advanced cases with marked bony involvement, abscess formation or paraplegia, regardless of prior or active tuberculosis.

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Author: Carles Pigrau

QUESTION 2: Should routine methicillin-resistant *Staphylococcus aureus* (MRSA) screening be in place prior to spine surgery?

RECOMMENDATION: Routine MRSA screening should not be performed prior to spine surgery. However, in hospitals with a high incidence of *S. aureus* spinal surgical site infection (SSI) and particularly high rates of MRSA infections, MRSA screening might be useful.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 7%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

According to a recent review of 161 studies, the pooled average of SSI in spine surgery was 1.9% (range: 0.1 to 22.6%) [1]. Instrumented spinal fusion had the highest rate (3.8%), followed by spinal decompression (1.8%) and spinal fusion (1.6%). *S. aureus* contributed to almost 50% of spinal SSIs with a range of 0.02 to 10%. Among *S. aureus* spinal SSIs, the pooled rate of MRSA infections was 38% [1]. The 30-day mortality rate among patients with SSI was 1.06%, double that of those without SSI (0.5%), with mortality increasing with the complexity of spinal surgery or with the presence of underlying diseases [2]. Moreover, SSIs increased re-admission rates (from 20–100%), reoperation rates (with a pooled average of 67%) and doubled health-care costs [1].

Preoperative nasal carriage of *S. aureus* has been shown to be a risk factor for SSI, but rates have been variable between studies [3,4]. Nasal decolonization with the use of topical mupirocin is utilized in 90% of cases, however, the impact of using this strategy on the reduction of SSIs in orthopaedic surgery have reported conflicting results [5,6]. A recent meta-analysis of all published studies in cardiac and orthopaedic surgery suggested that decolonization was associated with a significant decrease in *S. aureus* SSIs when either the intervention was applied to all patients or only to those who were nasal carriers [7]. Another meta-analysis showed that an absolute reduction in SSIs of 1% may be cost-effective, however, universal decolonization may increase the risk of mupirocin resistance [8].

In a not-yet published retrospective study of 1,749 patients scheduled for elective instrumented neurosurgery, the MRSA colonization rate was 0.74%. After decontamination, all MRSA carriage was eliminated and none of the 13 MRSA carriers developed an SSI, while only 1 MRSA-negative case developed a MRSA SSI.

In a recent retrospective study of 4,973 consecutive spine patients who were given cefazolin as prophylactic antibiotic therapy rather than topical nasal antibiotics for decolonization, 49 (1.1%) were MRSA carriers, and 94 (2.1%) developed an SSI, 11 of which were caused by MRSA [9]. The SSI rates were similar in nasal carriers compared to non-MRSA carriers (3 of 49 vs. 91 or 4,433, $p = 0.13$) and nasal carriage was not a risk factor for spinal SSIs.

In conclusion, in patients undergoing spinal surgery, the low level of MRSA carriage and MRSA SSI are arguments against routine MRSA screening. In hospitals with a high incidence of *S. aureus* spinal SSI and high rates of MRSA infections, MRSA screening could be useful.

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Authors: Alexander Vaccaro, Barrett Boody

QUESTION 3: Is there a role for routine decolonization of patients undergoing spine surgery? If so, what is the optimal agent(s)?

RECOMMENDATION: There is evidence to support the use of institutionalized screening and decolonization programs in methicillin-resistant *Staphylococcus aureus* (MRSA) carriers to reduce the rate of surgical site infection (SSI), however the optimum agents for decolonization have not been determined.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 91%, Disagree: 0%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

There is evidence to support the use of institutionalized screening and decolonization programs to reduce the rate of SSI, however the optimum agents for decolonization have not been determined [1]. Preoperative nasal MRSA colonization is associated with increased risk postoperative spinal SSI. Thakkar et al. reported screening positive MRSA SSI rates of 12% compared with screening positive for MSSA (5.73%) and screening negative (1.82%) [2]. Furthermore, Ramos et al. found increased rates of SSI in hip and knee arthroplasty and spine fusions, reporting a 4.35% SSI rate in colonized (nasal MRSA and MSSA) patients versus a 2.39% rate in noncolonized patients [3].

While widely utilized preoperatively, there is minimal evidence specifically supporting the use of chlorhexidine gluconate (CHG) showers preoperatively. The 2015 Cochrane review written by Webster et al. reported minimal evidence supporting isolated use of CHG showers preoperatively. Four reviewed trials comparing CHG to placebo found no effect, and only one trial comparing CHG showers to controls reported an improvement in SSI rate [4].

The majority of reviewed literature bundles the use of nasal decolonization with other interventions (CHG wipes, CHG showers, etc.). Multiple reviews on the effectiveness of bundled interventions for decolonization in surgical patients (including orthopaedic surgery) report reduced SSI rates with nasal decolonization and CHG wipes [5,6]. Reported studies on nasal decolonization protocols have largely shown benefit in reducing SSIs. Mullen et al. used CHG wipes and alcohol-based nasal decolonization preoperatively and reported a mean reduction rate in SSI of 81% (1.76 per 100 to 0.33 per 100) [7].

Chen et al. reviewed 19 studies of decolonization protocols on orthopaedic procedures and found significant efficacy in reducing SSIs, reporting reduction of *S. aureus* SSIs ranging from 40–200% and reduction of MRSA SSI from 29–149% [8]. Bode et al. performed a randomized, double blinded trial to determine if decolonization would reduce the SSI rate. Of 6,771 general, orthopaedic and neurologic surgery patients, 18.5% tested positive for *Staphylococcus* and were decolonized with 5 days of CHG showers and mupirocin nasal ointment. SSI rates significantly reduced from 7.7 to 3.4% using eradication compared with the placebo control [9]. These interventions are likely cost-effective as well, as Slover determined that the cost-efficacy threshold for their institution's screening and decolonization protocol would be met with a spine SSI reduction of only 10% [10].

It is our recommendation that patients who screen positive for nasal MSSA and MRSA should be decolonized using 2% mupirocin ointment applied intranasally and 2% chlorhexidine gluconate (CHG) showers for five days preoperatively. Additionally, in patients positive for MRSA, intravenous vancomycin 15 mg/kg should be administered preoperatively prior to skin incision and for 24 hours postoperatively.

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QUESTION 4: How should patients currently using disease-modifying antirheumatic drugs (DMARDs) be managed in the perioperative period?

RECOMMENDATION: Spine surgeons caring for patients with rheumatic diseases must be aware that there are specific issues involved in their perioperative management. The optimal strategy for managing DMARD medications during the perioperative period of spine surgery is unknown due to the lack of evidence and it is largely based on low-quality evidence and expert opinion. A rheumatologist should be involved in the medication management around the time of surgery.

1. For nonbiologic DMARDs such as methotrexate (MTX), leflunomide, hydroxychloroquine and/or sulfasalazine, continuation of the current dose throughout the perioperative period is recommended.
2. For biologic DMARDs such as etanercept, we recommend that physicians withhold the biologic medication and plan elective surgery at the end of the dosing cycle for that specific medication. As an example, patients taking a weekly dose should schedule the surgery in the second week after the first withheld dose. These agents should not be restarted until external wound healing is complete, which is typically around two weeks. Exception: In patients taking tofacitinib (twice daily dose), withholding of tofacitinib for at least one week prior to surgery is recommended.
3. For medications typically used for systemic lupus erthematosus (SLE) patients, such as mycophenolate mofetil, azathioprine, cyclosporine and tacrolimus, the decision to withhold medications prior to surgery should be made on an individual basis.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Nonbiologic DMARDs

Although a reasonable concern exists about the potential of nonbiologic DMARDs to increase the risk of infection by affecting the immune response [1,2], stopping DMARDs prior to surgery may result in a flare-up of disease activity, which may adversely affect rehabilitation. Therefore, we suggest that patients continue the current dose of nonbiologic DMARDS throughout the perioperative period, including methotrexate (MTX), leflunomide, hydroxychloroquine and/or sulfasalazine. In clinical practice, the nonbiologic DMARD dose is often missed for one day and up to three days while the patient is hospitalized. Several studies of rheumatoid arthritis (RA) patients undergoing elective orthopaedic surgery have found that continued use of MTX through the perioperative period is safe [3,4]. A systematic review including four studies with RA patients undergoing elective orthopaedic surgery evaluated the effects of continuing MTX versus stopping MTX in the perioperative period [5]. Continued MTX therapy was safe perioperatively and was associated with a reduced risk of flares. There was no evidence to suggest that stopping MTX preoperatively reduced the incidence of infection or improved wound healing. However, in all of the studies, the mean dose of MTX was less than 15 mg per week.

The limited data on the use of leflunomide during the perioperative period is conflicting [6,7]. In one study, there were significantly more wound complications in patients taking leflunomide at the time of elective orthopaedic surgery compared with patients on MTX [7].

There are also limited data suggesting it is safe to continue hydroxychloroquine and sulfasalazine in the perioperative period. In a retrospective study of 367 orthopaedic surgeries among 204 RA patients, two-thirds of whom were receiving nonbiologic DMARDs including hydroxychloroquine and sulfasalazine, there was no increased infection associated with nonbiologic DMARD use [8].

Biologic DMARDs

We recommend that surgeons withhold biologic medication and plan the elective surgery at the end of the dosing cycle for that specific medication. As an example, patients taking weekly etanercept should aim to schedule the surgery in the second week after the first withheld dose. Patients taking adalimumab in two-week intervals should plan the surgery in the third week after the first withheld dose. In a similar manner, patients on monthly intravenous abatacept should schedule the surgery in the fifth week after the first withheld dose. Patients taking rituximab should wait until month seven after the last dose to schedule the surgery, presumably when B cells have returned to the circulation. However, nonelective procedures should not be delayed in patients who have been recently treated.

There is relatively little evidence available regarding the optimal timing for use of biologic DMARDs in the perioperative period, and our recommendation is largely based on indirect evidence suggesting an increased risk of infection associated with their use [9–11]. Many [12–16], but not all [17,18] retrospective studies suggest that use of tumor necrosis factor (TNF) inhibitors do not increase the risk of postoperative infections or impair wound healing.

The infectious risks of abatacept are similar to those of TNF inhibitors and other biologic agents, but there are no trials that have examined abatacept's safety perioperatively [9,19]. A case series described eight uncomplicated surgeries in seven RA patients on abatacept [20]. Similarly, there is no direct evidence regarding the safety of the interleukin (IL)-1 receptor inhibitor anakinra in the perioperative period. Conclusions regarding perioperative safety are largely based on trials in nonoperative patients showing that the infection rate was similar to that in patients receiving placebo [21].

These agents should not be restarted until external wound healing is complete, which is typically around two weeks. There is no evidence regarding the optimal time to restart biologic DMARDs in the perioperative setting and this approach is based on standard precautions used for biologic agents that warn against use in patients with active infection, such as an open wound.

Antirheumatic Kinase Inhibitor

In patients taking tofacitinib, we (Fang et al.) withhold the medication for at least one week prior to surgery. Tofacitinib is an orally-administered Janus kinase (JAK) inhibitor that is used in the management of patients with moderately to severely active RA. Our recommendation is based on indirect evidence from systematic reviews and meta-analyses of tofacitinib in nonsurgical patients showing there is an increased risk of infection with tofacitinib compared with placebo. Although the half-life is thought to be short for tofacitinib, there is uncertainty regarding the duration of immunosuppression after the drug is held [22].

Other SLE-specific Medications

There is uncertainty regarding the optimal perioperative medication management in patients with SLE given the lack of data. More data are needed to help guide perioperative medication management in lupus patients, including information on hydroxychloroquine, MTX, mycophenolate mofetil, azathioprine, cyclosporine and tacrolimus. Given the clinical spectrum of SLE disease severity and organ involvement, the decision to withhold medications prior to surgery should be made on an individual basis. Thus, for patients with severe SLE and multi-organ involvement in which discontinuation of the medication may result in a disease flare, it is reasonable to continue the medications through the surgical period. This is based on indirect evidence from organ transplant patients that supports continuing anti-rejection therapy during the time of surgery [23,24].

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QUESTION 5: Is postoperative hyperglycemia a risk factor for the development of infection following spinal surgery?

RECOMMENDATION: From the limited evidence, the association between postoperative hyperglycemia and surgical site infection (SSI) remains unclear and further study is needed.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 7%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

Postoperative hyperglycemia does not only occur in patients diagnosed with diabetes mellitus (DM). Only 41% of patients with serum glucose levels greater than 200 mg/dL were identified in the medical records with the diagnosis of diabetes [1]. Langlois et al. suggested that non-diabetic patients experienced a statistical increase in blood glucose levels in the first three days following spine surgery [2]. They also pointed out the possibility of blood glucose elevation in non-diabetic patients associated with postsurgical complications. After major surgery, perioperative blood glucose elevations may be associated with previously undiagnosed DM, or occur because of the activation of the hypothalamic-pituitary axis, a physical response to severe stress in individuals at risk [3].

DM is a disease of uncontrolled hyperglycemia, which impairs the immune system. The wound healing in patients with diabetes is impaired as a result of microangiopathic changes and ischemia, impaired granulocyte function and a lack of platelet-derived growth factor function in the wound [4]. Despite the lack of multiple randomized clinical trials, various retrospective studies have found that DM is strongly associated with SSI after spinal surgery [5–16]. Moreover, DM increases the risk of not only SSI but other postoperative complications such as urinary tract infection, unplanned readmission and prolonged length of stay [17–19].

From a retrospective case-control study of patients who underwent an orthopaedic spinal operation performed at a university-affiliated tertiary care hospital, the risk of SSI, the odds ratio for postoperative hyperglycemia (> 200 mg/dL), was 2.9 (95% confidence interval (CI): 1.2, 6.5) after univariate analyses. But, the risk did not remain significant after multivariate logistic regression analysis [11]. A retrospective case-control study evaluating 104 patients with SSI after spinal surgery matched with 104 randomly-selected control patients without SSI after spinal surgery, revealed that patients with postoperative glucose measurements greater than 126 mg/dL within 48 hours after surgery were significantly more likely to develop an SSI than patients without an elevated glucose measurement on univariate analysis (crude odds ratio: 3.2, 95% CI: 1.6, 6.3). But, it was not significant after adjusting for other variables [20]. A retrospective case-control study evaluating specific independent risk factors for SSI after laminectomy or spinal fusion at a tertiary care hospital affiliated with a university hospital, identified that high serum glucose (> 200 mg/dL) at any time during hospitalization was significantly associated with SSI in the univariate analysis (odds ratio: 3.0, 95% CI: 1.4, 6.3) [1].

On the other hand, a retrospective study evaluating perioperative variables to determine the risk factors for SSI in a total of 2,715 patients undergoing posterior lumbar spinal surgery revealed that high preoperative serum glucose (odds ratio: 1.169, 95% CI: 1.016, 1.345) and a history of DM (odds ratio: 2.227, 95% CI: 1.100, 4.506) were associated with SSI in multivariate logistic regression analysis, although postoperative serum glucose level showed no association [21]. In another retrospective study using the Nationwide Inpatient Sample (NIS) database, uncontrolled DM revealed a higher risk of postoperative infection (odds ratio: 4.90, 95% CI = 2.84, 8.46) than controlled DM (odds ratio: 1.91, 95% CI: 1.54, 2.37) [7]. But, there was no ICD-9-CM coding standard or parameter in the clinical setting that provides standardization of "uncontrolled" or "controlled" diabetic patients. Furthermore, the NIS does not provide quantitative data on blood glucose levels or hemoglobin A1c (HbA1c) percentage, making it impossible to further stratify cohorts based on overall control of a patient's diabetic condition.

Limited evidence supports the association between perioperative HbA1c and SSI [22,23]. The cut-off values for HbA1c differ among studies and the results were originated from small retrospective studies without multivariate analyses. Larger prospective studies are needed to confirm the association.

Though DM is strongly related to SSI in spinal surgery, no observational studies were able to reveal a significant association between postoperative hyperglycemia and SSI in multivariate analyses. From the limited evidence, the association between postoperative hyperglycemia and SSI remains unclear, and further study is needed on this issue.

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QUESTION 6: Is there an association between urinary tract infection (UTI) and surgical site infection (SSI) following spinal surgery?

RECOMMENDATION: Evidence regarding an association between UTI and SSI following spine surgery is conflicting and no convincing relationship has been proven. In a like fashion, no convincing relationship has been established between asymptomatic bacteriuria and SSI following spine surgery.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 71%, Disagree: 21%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

The treatment of organisms isolated from urine culture in the setting of orthopaedic surgery with hardware implantation is controversial and has been often driven by anecdote. The risk of seeding of hip and knee arthroplasties from asymptomatic bacteriuria has been studied and found to be small, with no cases in two studies [1,2]. A systematic review of the topic concluded that there was no evidence to support a direct causal relationship between perioperative asymptomatic bacteriuria and arthroplasty infection [3].

Data from the American College of Surgeons National Surgical Quality Improvement Program suggests that UTIs occur in nearly 1 of 50 patients undergoing posterior lumbar fusion procedures [4]. However, there are few studies that directly address a relationship between UTI and SSI in instrumented spine surgery. Nunez-Pereira et al. studied 466 patients, of whom 89 had UTIs and 54 had SSIs, with 22 patients having both [5]. Of these 22, the same organism was isolated from the surgical site and urine in nine patients. UTI conferred an odds ratio (OR) of 3.1 for SSI, though the statistical analysis recognized all UTIs and not just infections with the same organism. Tominaga et al. studied a cohort of 825 patients with 14 patients who developed SSIs and 20 patients who developed UTIs, and found no association between SSI and UTI [6].

It seems germane as well to address the relationship of asymptomatic bacteriuria and postoperative spine infection. Lee et al. studied 355 women > 65 years of age undergoing spine surgery [7]. Of these, 42 developed asymptomatic bacteriuria, with no association with SSI. A statistically significant association was found between asymptomatic bacteriuria with a Foley catheter in place and infection in patients who had undergone instrumentation of multiple levels. However, of 15 patients with postoperative infections, only 2 had the same organism (*Staphylococcus epidermidis* in both cases) isolated from cultures of surgical site and urine.

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Authors: Alexander Montgomery, Daniel Tarazona

QUESTION 7: What are the risk factors predisposing a patient to surgical site infections (SSI) after spine surgery?

RECOMMENDATION: Numerous risk factors for SSIs following spine surgery have been identified, including diabetes, obesity, prior SSI, smoking, longer operative times, posterior approach to spine and the number of levels fused.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The relatively low incidence of postoperative SSIs after spine surgery makes it challenging for studies to evaluate the risk factors for SSI in a prospective manner [1]. Based on our literature search, a number of retrospective studies and a single prospective study were identified. The findings of prior studies have also been summarized by multiple systematic reviews. Pull ter Gunne et al. performed a systematic review of 24 studies that identified risk factors for SSI after spine surgery [2]. All 24 studies were case-control and case series. There was a total of 73 potential factors evaluated, 34 of which were found to be significant in at least 1 study. There were 11 risk factors that were found to be significant in at least 2 studies. Among all risk factors, diabetes, obesity and prior SSI were the only three that were confirmed as risk factors by a multitude of studies.

Similarly, there was another systematic review which analyzed 36 observational studies for which 46 independent factors were studied [3]. Only six risk factors had been consistently proven to show an association with SSI after spine surgery, including diabetes, obesity, longer operative time, smoking, history of SSI and type of surgical procedure (i.e. tumor resection).

More recently, a prospective multicenter surveillance study was performed which enrolled 2,736 patients who underwent posterior thoracic and/or lumbar spine surgery [4]. Of these patients, 24 (0.9%) developed postoperative deep SSI. Preoperative steroid therapy, spinal trauma, male gender and prolonged operating time (> three hours) were found to be independent risk factors for SSI after spine surgery. Several previous retrospective studies have not identified preoperative steroid use and male gender as risk factors for SSI after spine surgery [2,5,6].

An ongoing prospective study funded by Pfizer evaluating the potential role of vaccination against *Staphylococcus* is likely to provide valuable information regarding the most important risk factors for SSI after spine surgery.

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Authors: Claus Simpfendorfer, Pouya Alijanipour, Caroline J. Granger

QUESTION 8: Should all patients with psoas abscesses be screened for both spine and hip infections?

RECOMMENDATION: Cross-sectional imaging with computed tomography (CT) and magnetic resonance imaging (MRI) will identify the source of secondary psoas abscesses in the majority of cases. If no other source is identified, consider cross-sectional imaging with CT or MRI for both the hip and spine in the setting of psoas abscess.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain 0% (Unanimous, Strongest Consensus)

RATIONALE

The iliopsoas is formed by two distinct and separate muscles - the psoas major and iliacus muscles. Each muscle is covered by its respective fascia and is typically associated with different disease entities [1]. The psoas major arises from the transverse processes of the lumbar vertebrae, exiting the pelvis beneath the inguinal ligament where it joins the iliacus (forming the iliopsoas tendon) and inserts on the lesser trochanter of the femur [2]. The iliacus muscle originates from the superior portion of the iliac fossa, superior lateral aspect of the sacrum and ventral sacroiliac and iliolumbar ligaments [2]. The medial portion of the iliacus muscle joins the psoas major tendon (forming the iliopsoas tendon) and inserts on the lesser trochanter. The lateral portion of the muscle inserts

directly on the anterior and anteromedial aspect of the femur below the lesser trochanter [3].

The literature often does not delineate between the two muscles, referring to the combined muscles as the iliopsoas or simply the psoas muscle. Making a distinction between these muscles can help determine the source of infection. With regards to musculoskeletal infections, the majority of psoas muscle abscesses reflect extension from an adjacent spondylodiskitis or septic facet [4–7]. In contrast, iliacus muscle abscesses are secondary to extension of an underlying hip infection through the iliopsoas bursa or infectious sacroiliitis.

The iliopsoas bursa is the largest bursa in the body and communicates with the hip joint in 14% of the population [8]. Communication of the joint capsule with the iliopsoas bursa is likely increased following hip arthroplasty [9]. With the majority of the bursa located deep in the iliacus muscle, hip joint infections typically involve the iliacus muscle alone or less often both the iliacus and psoas muscle [1,10]. When the psoas muscle is involved, there should be visible communication with a distended iliopsoas bursa. This is in contrast to the psoas abscess associated with spondylodiscitis, which does not involve the bursa.

Both lumbar spine osteodiscitis and septic hip arthritis can be associated with psoas abscess [11]. The spine as primary source of infection for secondary psoas abscess should always be included in the differential diagnosis [12]. Studies have reported that 10–36% of secondary psoas abscess is caused by disc infection [13,14]. The anatomical proximity and communication of the psoas muscle to the hip joint capsule creates a potential transit for bacterial spread from spine to the hip joint or vice versa [15]. Screening patients with a psoas abscess for both hip and spine infection can prevent this harmful infectious spread. However, it should also be considered that the infection may simultaneously result in multiple infection sites from the same original hematogenous source of psoas abscess or spinal infection.

A non-coincidental association exists between psoas abscess and hip infection, both in the virgin hip joint and in a prosthetic hip joint. There have been multiple reports regarding the progression of the extension of psoas abscesses into the virgin or prosthetic hip joints [16–19]. In one study, the percentage of prosthetic hip infections with associated psoas abscesses has been reported to be as high as 12% [19]. Hematogenous prosthetic infection and a medical history of neoplasm have been reported as risk factors of psoas abscess in patients with an infected hip replacement [19]. Psoas abscesses may also cause relapse of prosthetic hip infection.

It is recommended that practitioners screen patients with psoas abscesses for hip infection and spinal infection due to their anatomical communication, relationship in etiology and co-prevalence. Clinicians should be aware of the potential communication between the lumbar spine and hip joint via the psoas muscle and iliopsoas bursa. Successful treatment outcomes of psoas abscess are not only related to its early diagnosis, but also to the prompt detection of its spread to adjacent organs with potentially devastating outcomes, including the neural elements of spine and a prosthetic hip joint.

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1.5. PREVENTION: WOUND CARE

Author: Carles Pigrau

QUESTION 1: Is negative pressure wound therapy (NPWT) safe on spinal wounds in patients with a cerebrospinal fluid (CSF) leak?

RECOMMENDATION: NPWT may be harmful in patients with a CSF leak, leading to severe neurological sequelae.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 7%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

Intracranial hypotension may develop after dural puncture or spinal surgery by accidental intraoperative opening of the dura. As a complication to this, several cases of accidental drainage after spinal surgery and application of negative pressure suction devices (NPSDs) have been reported [1–4]. Secondarily, intracranial hypotension may develop leading to tonsillar herniation, subdural hemorrhage, severe neurological sequel and even death.

Recently, Sporns et al. reviewed the literature published in reference to patients diagnosed with postsurgical or post-traumatic intracranial hypotension [1,4]. In 24 relevant reports that included 27 cases, in 15 cases a NPSD (including NPWT or pleural drainage after thoracic surgery or traumatism) was applied, ten had no negative pressure devices and two could not be determined for application of a suction drain. All patients with NPSD had severe neurological symptoms, while only mild symptoms were observed in cases without such devices. They concluded that the increasing use of NPSDs causes the reported condition and that acute intracranial hypotension should be considered as an explanation of postoperative neurological symptoms or coma after cranial or spinal surgery. A precise radiological examination (preferably with magnetic resonance imaging) can help to rule out intracranial hypotension and dural laceration.

In conclusion, in patients with spinal wounds, NPSDs (including pleural drainages) may be harmful and lead to more severe neurological sequel than those cases with liquoral hypotension secondary to dural laceration without negative pressure devices.

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Author: Barrett Boody

QUESTION 2: What are the risks and benefits for the use of vacuum-assisted closure (VAC) devices/PICO dressings following spine surgery?

RECOMMENDATION: The use of incisional VAC therapy (such as PICO dressings) is limited, but available literature supports its use in the prevention of dehiscence and surgical site infection (SSI) in posterior thoracolumbar deformity surgery.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 14%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

Multiple case series and case reports have been published supporting the use of VAC therapy for staged treatment of deep/subfascial SSI in spine surgery, with the common use being at index or second debridement, followed by multiple VAC changes until the wound is suitable for closure [1–4]. The specific VAC techniques (such as fascia open or closed, number of suction devices, suction settings, etc.) is poorly described in available studies. Ploumis reported on 73 patients undergoing VAC therapy for deep SSI, noting an average of 1.4 procedures following VAC placement (including closure) and closure of wound at an average of 7 days. They noted that methicillin-resistant *Staphylococcus aureus* (MRSA) and polymicrobial wound infections were more likely to require subsequent debridement after index VAC placement prior to definitive closure [2]. Similarly, Mehbod described 20 similar patients with deep SSI following spine surgery treated with VAC therapy, with an average of 2.2 procedures (including closure) following index VAC placement and resolution of infection in all patients and closed wounds by 6 months [3]. Canavese described 33 pediatric patients treated with VAC therapy for deep SSI after thoracolumbar spine surgery, with only 1 case ultimately requiring partial removal of implants [5].

Complications for VAC therapy have also been widely described, including need for reoperation and/or revision of hardware, bleeding, flap closure or skin grafting, retention of foam sponge fragments and cerebrospinal fluid (CSF) leaks resulting in neurologic complications (coma, brain herniation and intracranial hemorrhage) [1,2, 6–8]. The use of VAC therapy in the setting of CSF leak should be avoided due to risks of tonsillar herniation [7]. While VAC therapy over dura has been described in cranial surgery, no publication specifically described the application of sponges over dura in spine surgery. Multiple cranial publications describe the technique for dural application as the use of the "white" sponge (polyvinyl foam), as it is hydrophilic and less adherent, with lower suction pressures (~ 50 mmHg) [9,10].

The only available paper on the application of incision VAC therapy (such as PICO dressings) for spine surgery was published by Adogwa et al., who reviewed 160 posterior thoracolumbar deformity surgeries, of which 46 used incisional negative pressure wound therapy for 3 days. The authors reported lower rates of wound dehiscence (6.38% vs. 12.28%) and lower SSI rates (10.63% vs. 14.91%) for the incisional negative pressure wound therapy group, both reaching statistical significance ($p < 0.05$) [11].

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Author: Jeffrey A. Rihn

QUESTION 3: What type of surgical dressing is most effective for lowering rates of surgical site infection (SSI) in patients undergoing spine surgery?

RECOMMENDATION: There are no randomized studies comparing the use of incisional negative pressure wound therapy (NPWT) to standard dry dressings in spine surgery. The World Health Organization (WHO) recommends the use of incisional NPWT for high risk surgical wounds to reduce the risk of SSI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 0%, Abstain: 14% (Super Majority, Strong Consensus)

RATIONALE

Incisional NPWT in the form of commercially available incisional suction dressings has recently gained popularity in the management of high-risk wounds in orthopaedic surgery.

These dressings are used at the time of index surgery primarily, with the aim of preventing wound complications such as SSI. Incisional NPWT protects the healing wound by preventing wound edge motion, improving of blood supply, removing of excess fluid and stimulating granulation tissue. A recent meta-analysis of all randomized and case-controlled trials comparing incisional NPWT to standard of care showed a reduction in SSI (50%), wound dehiscence and hospital length of stay [1]. In a pig spine model, Glaser showed improved early biomechanical properties as well as cosmesis in wounds dressed with incisional NPWT compared to standard dry dressings [2].

There are only two studies that have investigated incisional NPWT after spine surgery. A single-institution retrospective case-control study from Duke University showed a 50% decrease in wound dehiscence and a 30% decrease in SSI after a change to incisional NPWT dressing for thoracolumbar deformity wounds [3]. Similarly, a small randomized trial by Nordmeyer et al. showed a decrease in seroma and the need for nursing wound care intervention in patients who were treated with incisional NPWT [4]. The authors hypothesized that a decrease in seroma may lead to decreased SSI, but the study was underpowered to show this difference.

The 2016 WHO recommendations on intraoperative and postoperative measures for SSI prevention proposed prophylactic NPWT on primarily closed surgical incisions in high-risk wounds to reduce the incidence of SSI [5]. This recommendation drew on evidence from abdominal, thoracic and orthopaedic surgery.

In the absence of high-quality randomized trials and given the WHO recommendation, it would be reasonable to use incisional NPWT in settings where the surgeon believes the wound is at risk of infection or breakdown. Spine wounds at high risk of infection include those in patients with diabetes, increased BMI, extended operative times and chronic steroid use [6,7]. In the pediatric spine population, risk factors for SSI include high weight centile, neuromuscular scoliosis, greater comorbidities and prolonged operative time [8].

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Diagnosis

2.1. DIAGNOSIS: GENERAL PRINCIPLES

Authors: Robert Sawyer, Joseph K. Weistroffer, Anna White

QUESTION 1: What is the definition of surgical site infection (SSI) in spinal surgery?

RECOMMENDATION: We recommend utilizing the definition provided by the Centers for Disease Control and Prevention (CDC), National Healthcare Safety Network (NHSN) Patient Safety Component Manual, Chapter 9: Surgical Site Infection (SSI) Event.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The most persuasive argument for adopting the CDC's definition for an SSI lies in utilizing search protocols to map International Classification of Disease, 10th revision, Procedure Classification System (ICD-10-PCS) and Current Procedural Terminology (CPT) codes when querying databases.

The CDC definition is the accumulation of multiple years of planning/tracking and modifying this instrument via annual reviews and input from professionals worldwide. The description includes such categorical sub-elements as the definition of an operative procedure and the definition of an operating room. It includes criteria for the sub-classifications of a superficial incisional SSI, deep incisional SSI and organ/space SSI [1]. The CDC's definition delineates the exclusion of such events as cellulitis, stitch abscesses, as well as stab wound or pin site infections. It also defines such infections about primary or secondary wounds and the surveillance periods for SSI following operative procedures. Furthermore, numerous spine-related studies have utilized the same definition put forth by the CDC [2–5].

Adopting a thorough and uniform definition for SSI is imperative, as studies have shown that the rate of SSI following spine surgery varies based on the definition used [6]. In addition, having a standardized definition will improve surveillance, provide consistency among studies and improve overall patient care.

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Author: Claus Simpfendorfer

QUESTION 2: What defines delay in the diagnosis of a spine infection?

RECOMMENDATION: There is no clear or established definition of delayed diagnosis for spine infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The diagnosis of spinal infections is often delayed from one to three months from the onset of symptoms [1,2]. Delay in diagnosis is frequently secondary to nonspecific symptoms including back and neck pain. A couple of studies have used delayed diagnosis

of greater than eight weeks as a predictor of lower recovery rates, neurologic deficits and long-term disability [2–4]. A recent study by Issa et al. demonstrated that the percent of positive cultures from blood and/or biopsy decreases as the delay in diagnosis increases [2–5].

Jean et al. looked at predictors of delayed diagnosis and found that X-rays resulted in an increased delay from 14 days to 34.7 days [6]. It is presumed that, although delaying diagnosis, X-ray findings (either normal or demonstrating degenerative changes) provide the physician with reassurance. Alternatively, Jean et al. found that fever at initial presentation, elevated C-reactive protein (CRP) and blood cultures shortened the time to diagnosis [6]. The most significant impact was the elevated CRP which shortened the diagnostic delay from 73 days to 17 days [6]. It is therefore suggested that CRP be routinely checked in cases of new onset or sudden increased back pain [6,7]. Furthermore, if CRP is elevated or if there is clinical suspicion for spine infection, MRI with gadolinium should be performed [8].

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Authors: John Koerner, David Kaye

QUESTION 3: Is there an optimal window for diagnosis of an early spine infection?

RECOMMENDATION: There is no defined window, but early diagnosis of a postoperative spine infection (up to three months from time of surgery) treated with surgical debridement and antibiotics often allows for retention of instrumentation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 7%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

Although the evidence regarding this topic is from low-quality studies, the findings and recommendations are consistent. Most postoperative spinal infections in adults present early, typically within the first three months [1]. Early diagnosis and debridement typically allows for retention of implants when present [1]. Implant removal due to infection can result in satisfactory results and eradicate infection, but can lead to malalignment and pseudarthrosis [2].

Early spine infections (< three months after surgery) treated with irrigation and debridement have improved outcomes compared to before surgery, but cause increased back pain and a lower probability of achieving a minimal clinically important difference [3].

In a cohort study of 51 patients who developed a postoperative spinal implant infection, prompt treatment (< 3 months) with debridement allowed for implant preservation in 41 patients, versus 10 patients in which treatment was delayed and implants were removed [4]. Another case series identified 26 postoperative infections, of which 24 were able to be treated without removal of implants by aggressive debridement and secondary closure [5]. Early identification and treatment can often allow for implant retention compared to delayed presentation, when implants may need to be removed [6–8].

Late spine infections are, however, seen more commonly in idiopathic scoliosis cases [9]. In a case-controlled series of 236 patients, seven developed an infection [10]. One was early and the other six were diagnosed at an average of 34.2 months postoperatively.

It is typical for patients to have symptoms of low back pain for 4 to 10 weeks prior to diagnosis of spondylodiscitis [11,12]. Although most studies recommend early treatment, no specific timeframe could be identified that definitely leads to better outcomes.

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Author: Gregory Schroeder

QUESTION 4: How do early and late infectious complications differ following spine surgery?

RECOMMENDATION: Early infections, defined as occurring within 30 days of surgery, often present with local signs of infection such as increased surgical site pain, erythema, warmth and wound drainage. Conversely, late infections (> 90 days after surgery) commonly present with an insidious onset of chronic pain and implant failure/ pseudarthrosis if following a fusion.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 87%, Disagree: 0%, Abstain: 13% (Super Majority, Strong Consensus)

RATIONALE

Postoperative spine infection occurs at a rate of 0.7–16% depending on the procedure; the lumbar spine is the site of 51% of infections [1].

A postoperative infection is classified as early when it occurs within 30 days of the initial surgery. Early infections typically present with increasing back pain (83–100%) as the primary symptom [2,3]. Fever, weight loss, erythema, swelling, warmth, tenderness and elevated white blood cell (WBC) count may also be present, with fever having an incidence of 16–65% [2–4]. One of the most reliable and specific signs of early infection is increased wound drainage (67%) as it can occur in both deep and superficial infections [4].

A postoperative infection occurring three to nine months following surgery can be classified as a late infection. As opposed to early infections, late infections typically present with delayed symptoms such as lack of adequate fusion, chronic pain or implant failure months after surgery [5]. Local symptoms may also occur, including increased pain and tenderness at the incision site. Wound drainage may occur but is less common than in early infections [5].

Complications of postoperative spine infection include impairment of function, significant morbidity and increased health care costs approximating up to $200,000 per patient [1,3]. Increase in hospital stay and increased rates of repeat surgery have also been observed.

Gram-positive bacteria, specifically *Staphylococcus aureus,* are responsible for approximately 45% of spine infections [6]. Other gram-positives such as *Staphylococcus epidermis* and *Enterococcus* as well as gram-negatives *Pseudomonas aeruginosa* and *Escheria coli* have been observed at lower incidences [1,2,6]. There is no clear association between type of surgical procedure and bacteria strain. However, gram-negatives tend to present more commonly in sacral and lumbar regions [6]. Fungal infections may occur in immunocompromised patients. *C. acnes* has recently been identified as another potential causative organism [2]. No significant difference has been observed in the type of organism present in early and late infections.

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Author: Bryan Alexander

QUESTION 5: Are there patients with degenerative pathology, such as disc herniations, who are actually infected with a low-grade infection (e.g., *Propionibacterium acnes*)?

RECOMMENDATION: The association between the *Cutibacterium acnes (C. acnes)* (formerly *P. acnes*) and degenerative spinal disease is inconclusive.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 14%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

The initial connection between potential low-level infection and degenerative spinal pathology was drawn when a group identified over half of discectomies performed for disc herniation as culture positive for *C. acnes* or coagulase-negative *Staphylococcus spp* [1]. A large number of predominantly small studies have since come to opposite conclusions on the connection between these bacteria and degenerative spinal disease, most commonly evaluated radiographically by the presence of Modic changes (examples of those finding no relationship [2–7] versus those finding a correlation [8–12]). One controversial placebo-controlled, double-blinded trial administered extended-duration antibiotic therapy to those patients with Modic type 1 changes and demonstrated better pain resolution in those receiving antibiotics [8].

Recent systematic reviews, each published in 2015, independently concluded that while there was strong evidence from multiple studies that patients undergoing spinal surgery have increased rates of bacteria at the site of degenerative disease of spine, causation between that finding and the pathologic changes resulting in back pain were unclear [1,13,14].

One important cause for heterogeneity in the data is the possibility that microbiologic sampling could be more readily contaminated with bacteria based on differences in surgical and collection technique [3,15]. However, this does not fully explain the fact that in clinical studies, *C. acnes* is consistently the most common, if not only, organism isolated. Recent studies, including control groups of patients not anticipated to have infectious etiologies for their spinal condition, have also noted increased rates of bacterial presence in degenerative disease compared to patients without degenerative disease [2,16]. Methods attempting to disrupt biofilm-encapsulated bacteria have attempted to explain negative culture results from earlier studies [10,17]. Similarly, molecular subtyping of *C. acnes* allows for better characterization of these isolates into those more likely to be routine skin contamination from those more likely to be pathogenic [2,17–19]. These studies have demonstrated a mixture of these subtypes present, with those generally not representing skin flora predominating. Recent studies have additionally investigated histologic methods [20], inflammatory cytokine responses [16,21] and proteomic analysis [22] in addition to bacterial presence as a marker for true infection. Finally, some groups have recently used animal models to attempt to support a connection between bacterial inoculation and symptomatic spinal pathology [23,24].

Though still unverified, there is an enlarging body of evidence using modern techniques and accounting for technical limitations in earlier studies for the role of infection in at least some types of degenerative spinal pathology. A well-designed, multicenter trial effort, which successfully confirms this connection would allow for reasonable consideration of further studies utilizing antibiotic therapy as a non-invasive therapy option for degenerative disc disease.

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QUESTION 6: What is the diagnostic algorithm of patients with suspected hematogenous vertebral osteomyelitis? Is the algorithm different for patients with tuberculosis (TB)?

RECOMMENDATION: We support the diagnostic algorithm for suspected hematogenous vertebral osteomyelitis per Infectious Disease Society of America (IDSA) Clinical Practice Guidelines, 2015. Diagnostic algorithm is not different for patients with TB.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 87%, Disagree: 6%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Vertebral osteomyelitis typically occurs due to hematogenous seeding of the adjacent avascular disc from a distant foci [1]. Appropriate management is contingent upon timely diagnosis. Patients with vertebral osteomyelitis are commonly misdiagnosed and treated for degenerative pathology [2]. This often leads to a delay in treatment on average from two to four months [3]. The diagnosis of vertebral osteomyelitis is not challenging in patients with acute onset low back pain and fever. In this circumstance the diagnosis can be confirmed with a serologic test and imaging studies. However, fever and leukocytosis occur in approximately 45% of patients with bacterial vertebral osteomyelitis and very rarely in those with fungal, brucellar or mycobacterial infections [4,5]. Vertebral osteomyelitis should be suspected in patients who have recalcitrant back pain in the setting of elevated inflammatory markers. In 2015, the IDSA published Clinical Guidelines for the diagnosis and treatment of native vertebral osteomyelitis (NVO) in adults [6,7]. These guidelines provide an algorithmic approach to the diagnosis of NVO based on a systematic review of the literature.

Obtaining a detailed history is a critical portion of the diagnostic algorithm and should include any recent travel, infections, open wounds, recent antibiotic treatment and intravenous drug use. Patients who have back pain and a history of bacteremia, particularly *Staphylococcus aureus,* should be suspected of having vertebral osteomyelitis; therefore, further work up is warranted in these scenarios [8–10]. Patients with vertebral osteomyelitis typically present with back pain exacerbated by physical activity. Pain may not be isolated to the affected area and can radiate to the abdomen, hip, leg, scrotum, groin or perineum [11]. A full physical examination should be performed and include assessment of motor and sensory function. It takes three to six weeks after the onset of symptoms for bone destruction to be evident on plain radiographs. Thus, normal images do not exclude diagnosis.

Magnetic resonance imaging (MRI) should be obtained in patients with suspected vertebral osteomyelitis, as it has a sensitivity of 97%, specificity of 93% and an accuracy of 94% in diagnosing vertebral osteomyelitis [12,13]. Gadolinium enhancement is critical to appreciate paravertebral or epidural involvement [14]. A repeat MRI should be considered in two to four weeks in a patient suspected of vertebral osteomyelitis whose initial imaging study failed to show features consist with the diagnosis [15]. Imaging features consistent with TB infections include destruction of two or more contiguous vertebrae, extension along the anterior longitudinal ligament and disc infection, with or without a paraspinal mass or mixed soft tissue fluid collection [16]. In patients for whom MRI is not possible, a spine gallium/Tc99 bone scan is an alternative with a sensitivity and specificity of around 90% for diagnosing vertebral osteomyelitis [17,18]. Positron emission tomographic scanning is also highly sensitive for detecting osteomyelitis [19].

Serologic testing is important in the diagnostic algorithm of vertebral osteomyelitis. A minimum of two blood cultures should be obtained for patients with suspected vertebral osteomyelitis [20]. Blood cultures should be incubated for up to two weeks and should include aerobic, anaerobic and fungal. Leukocytosis has low sensitivity and specificity in the diagnosis with approximately 40% of patients with osteomyelitis having a normal white blood cell (WBC) count [21]. However, an elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) in patients with back pain, though not specific, has a sensitivity that can range from 94% to 100% [22].

In patients with suspected vertebral osteomyelitis who reside in or have traveled to areas endemic for TB, a purified protein derivative (PPD) skin test can be performed; however, this test has a low sensitivity and specificity for diagnosis. An interferon-γ release assay has been shown to have a higher sensitivity than PPD, especially in immunocompromised patients with immune compromise [23]. Enzyme-linked immunospot assay has some diagnostic utility for TB and has been proven superior to PPD alone (sensitivity 82.8% vs. 58.6% and specificity, 81.3% vs. 59.4%, respectively) [24].

Empiric antibiotic therapy should not be initiated in aseptic patients without neurologic deficit until an image-guided biopsy can be obtained, especially if microbiologic diagnosis for a known associated organism has not been established by blood cultures or serologic tests [6]. Biopsy increases the likelihood of microbiologic diagnosis, improving the chance of successful medical management through targeted antibiotic therapy [25]. *S. aureus* bacteremia eliminates the need for biopsy, and antibiotics should not be delayed [8,22]. If biopsy is non-diagnostic, a repeat biopsy, image-guided or open biopsy, should be considered.

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Author: Taolin Fang

QUESTION 7: Should antibiotics be held prior to image-guided biopsy/aspiration for a suspected spine infection?

RECOMMENDATION: We recommend that prior to image-guided biopsy/aspiration for a suspected spine infection, all antibiotics should be withheld until after appropriate culture samples are obtained. Antibiotic administration, without aspiration/biopsy may be justified in patients who are critically ill and cannot withstand intervention or in patients with deteriorating neurological conditions.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 93%, Disagree: 0%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

The definitive diagnosis of spinal osteomyelitis can be made only with isolation of the organism from a positive blood culture or biopsy and culture of the tissues from the region of the infection. Spinal biopsies may be performed using computed tomography (CT) or fluoroscopy for guidance in localizing the site of the suspected infection. The identification of the infecting organism is useful in directing antibiotic therapy. In suspected infection of the spine, biopsy and culture of the tissues from the affected site has been reported to be successful in the identification of the infecting organism in 46–91% of cases [1–5].

In real practice, there are some instances where antibiotic treatment is empirically instituted before the patient has been biopsied. Such cases may include patients who have been on antibiotics for other infections such as pneumonia or patients with surgical implants and prior deep wound infections who are on chronic antibiotic therapy. Theoretically, retrieval of a pathogen from the disc space or vertebral body may be compromised by previous or ongoing antibiotic treatment. However, we were unable to identify any high-quality randomized clinical trial comparing the culture results of the image-guided biopsy between patients who received empirical antibiotic treatment versus those who did not have any antibiotic treatment prior to biopsy.

There has been a general consensus of opinion that antibiotics should be withheld prior to biopsy of the site of suspected infection in an effort to improve the yield of culture [6,7]. A study by Rankine et al. found that the yield of biopsy in isolating the infecting organism was lower at 25% in patients who had received antibiotics compared to 50% yield in patients who had not received antibiotics [8]. It is important to note that not all studies agree with the notion of withholding antibiotics prior to biopsy of the infected site. A recent study by Sehn et al. [9] reported that four of 14 patients with a high suspicion for infection, who were confirmed to have been treated with antibiotics within 3 days of their biopsy, had positive cultures. The yield of culture was not different from the cohort of 92 patients who had not received antibiotics (28.6% vs. 30.4%, $p = 0.86$). Both of the reports were retrospective non-randomized studies with a relatively small sample size.

In the absence of randomized prospective data, and using the logic drawn from other fields of orthopaedic study related to this

issue, we recommend that empirical treatment with antibiotics be withheld in patients with suspected infection of the spine until biopsy of site of suspected infection can be carried out. There are, however, circumstances (such as situations involving critically ill patients and those with deteriorating neurological status) in whom antibiotics may be started prior to the performance of biopsy.

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QUESTION 8: What is the incidence of infectious bacterial meningitis (PBM) following spinal surgery? Does the use of instrumentation affect this?

RECOMMENDATION: The incidence of PBM following spinal surgery varies from 0.1–0.4%. There is insufficient evidence to make any observations as to whether the use of instrumentation affects the incidence of PBM following spinal surgery.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

PBM is a potentially devastating complication following spinal surgery. It could occur after any primary elective spinal surgery with or without instrumentation, traumatic fracture-dislocation or surgical site infection after spinal instrumented surgery [1–3]. This also presents as a delayed complication after scoliosis surgery and through a dural tear with cerebrospinal fluid (CSF) leakage [4,5].

The early diagnostic differentiation from PBM and postoperative aseptic meningitis (PAM) is difficult and depends on CSF culture results [6–7]. The success in the treatment of patients with PBM depends on the stage of diagnosis, speed of diagnostic evaluation and appropriate anti-microbial and adjunctive therapy [8–9].

PBM is a potentially life-threatening infection with higher rates of mortality and significant disabling morbidity [9]. Pneumococcal meningitis is the most prevalent and is associated with a mortality of 30% [10]. PBM can also be caused by staphylococci [11], aerobic gram-negative bacilli (including *P. aeruginosa*) [12] and methicillin-resistant *Staphylococcus aureus* (MRSA) [13].

The incidence of PBM is rare after spinal surgery and is considered to be related to incidental durotomy [14]. Patients who have the triad of fever, neck stiffness and consciousness disturbance during postoperative period should be suspected and subjected to further evaluations [14]. In a large retrospective study, Lin et al. reviewed 20,178 lumbar spinal surgeries and reported a PBM rate of 0.10% [14]. Another retrospective study by Twyman et al. reported the incidence of PBM to be 0.18% after spinal operations with and without instrumentation [15]. The incidence could be as high as 0.4% after spinal surgery, when epidural abscess, subdural empyema, brain abscess, bone-flap infections and wound infections are combined [16].

In their sub-analysis, Lin et al. found that dural tears, pseudomeningocele and poor wound healing contributed to the majority of the complications [14]. The optimal management of PBM required reoperation to repair dural tears and administration of parenteral antibiotics [17]. The occurrence of pseudomeningocele is a sequela of dural tear, imperfect suture of the dura or fascia and inappropriate administration of antibiotics [14,18,19]. Zhang et al. reported surgical intervention to be an effective method of treating PBM where initial conservative measures failed. They proposed the idea that it is important to consider the possibility of PBM in any patient with CSF leakage after spinal surgery. They recommended early diagnostic imaging and CSF cultures to ensure prompt diagnosis and treatment [20].

Spinal instrumentation surgery usually involves longer operative time, greater blood loss and a higher incidence of subsequent SSI compared to decompression surgery alone. These features of spinal instrumentation surgery could influence the incidence of PBM. There is little literature examining the potential association of instrumentation with PBM with no supporting evidence linking the use of instrumentation to the incidence of infectious meningitis after spinal surgery [14,15,20]. Therefore, based on available evidence, it is not possible to link the use of instrumentation during spine surgery with PBM.

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Author: Taolin Fang

QUESTION 9: What are the early infectious complications after operations on the spine following the use of instrumentation?

RECOMMENDATION: Early infections are traditionally defined as those occurring within a month after surgery, typically becoming evident within two to three weeks of surgery. Recently, the definition has been broadened to include infection within 90 days of surgery.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 60%, Disagree: 20%, Abstain: 20% (Super Majority, Weak Consensus)

RATIONALE

Early infections are traditionally defined as those occurring within a month of surgery, typically becoming evident within two to three weeks of surgery. Recently the definition of early infection has been broadened to include infection within 90 days of surgery [1]. Surgical site infections (SSIs) and wound dehiscence are among the most common complications following spine surgery. It has been reported that the incidence of SSIs after adult spine surgery varies from 2–20% following instrumented procedures [2].

A study based on the American College of Surgeons' National Surgical Quality Improvement Program database reported that in a total of 99,152 spine surgery cases between 2012 and 2014, the overall wound complication rate was 2.2% with superficial SSI, 0.9% with deep SSI, 0.8% organ space SSI and 0.4% dehiscence: 0.3%. Of all the patients who experienced wound dehiscence, 46% had concomitant SSI. The average postoperative day of occurrence was 14 days with a standard deviation of 9 days (superficial SSI: 16 ± 8, deep SSI: 13 ± 10, organ/space SSI: 11 ± 10, dehiscence: 17 ± 8) [3].

Similar to other SSIs, early infections after spine surgery may present as pain, fever, erythema, swelling, warmth, tenderness and wound drainage. Local pain may herald the development of infection, particularly when it is escalating in nature. Wound drainage is common for both superficial or deep SSIs and may be present in up to 90% of patients [4].

Early postoperative spinal infections are most frequently due to relatively virulent pathogens such as *Staphylococcus aureus*, beta-hemolytic streptococci and aerobic gram-negative bacilli. *Staphylococcus aureus* is the most common bacteria responsible for early postoperative infection after spinal surgery [5–7]. The majority of the cases are due to methicillin-sensitive *Staphylococcus aureus* (MSSA), however the incidence of methicillin-resistant *Staphylococcus aureus* (MRSA) is escalating [8]. The majority of early infections are due to a single pathogen [9]. There has been an increase in the frequency of infections caused by gram-negative bacteria and other organisms such as *Pseudomonas aeruginosa*, *Escherichia coli*, Enterobacter and Acinetobacter [10–12].

Utilization of posterior instrumentation is well-recognized as a risk factor for the development of postoperative spinal wound infections. However, this finding is largely based on suboptimal retrospective analyses. Multiple factors increase the rates of infection following instrumented spinal surgery, such as increased wound exposure to air due to longer surgical time, greater soft tissue dissection, increased muscle/skin retraction, greater blood loss and potentially larger dead spaces [13–15].

However, anterior spinal exposures were reportedly correlated with a reduced risk of infection as they typically traverse relatively avascular tissue planes and avoid significant muscle dissection [16–19]. It is yet to be determined whether minimally invasive spine surgery is associated with lower infection rates versus open surgery following the use instrumentation [20–21], although a recent study involving 108,419 procedures reported that the use of a minimally invasive approach was associated with a lower rate of infection for lumbar discectomy (0.4% vs. 1.1%, $p < 0.001$) and for transforaminal lumbar interbody fusion (1.3% vs. 2.9%, $p = 0.005$) [22].

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2.2. DIAGNOSIS: BIOMARKERS

Author: Maja Babic

QUESTION 1: Are there any diagnostic tools that are useful for early surgical site infection (SSI) detection following spinal surgery? Does this differ whether or not there was instrumentation?

RECOMMENDATION: C-reactive protein (CRP) can be used to diagnose early SSI following spinal surgery.

A failure of CRP to decline or a second rise on postoperative days four to seven is a sensitive marker for infection following spine surgery, including both instrumented and non-instrumented spine surgery.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 86%, Disagree: 7%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

In a prospective study of 73 consecutive patients undergoing spinal decompression with and without instrumentation, inflammatory markers were assessed. They showed that following uncomplicated spinal surgery, CRP levels rise sharply, peaking on the second postoperative day [1]. Peak CRP values after instrumented lumbar surgery are significantly higher than those after non-instrumented spine surgery, but decline with the same half-life [1]. CRP was superior to erythrocyte sedimentation rate (ESR) in early detection of infections after cervical spine surgery, as shown in a prospective study of 51 cases [2]. In another large, prospective trial including 400 elective discectomy cases, CRP was shown to be a reliable, simple and economical screening test for infectious complications after lumbar microdiscectomy, superior to classical laboratory parameters. The sensitivity of serial CRP testing was calculated to be 100% with 95.8% specificity. ESR and white blood cell measurements fail to reach distinctive significance in diagnosing early SSI [3].

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Author: Maja Babic

QUESTION 2: When do common blood biomarkers such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) or Procalcitonin normalize after spine surgery?

RECOMMENDATION: Following spinal surgery with or without instrumentation, CRP values peak on days 2-3 postoperatively and normalize within 14 days. ESR also normalizes within 14 days.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 50%, Disagree: 29%, Abstain: 21% (NO Consensus)

RATIONALE

Multiple prospective studies suggest that CRP values peak within 2-3 days postoperatively (peak levels depend on extent of surgery, levels involved, etc.) and decrease back to baseline within 14 days. A rapid decline of CRP postoperatively is interrupted if postoperative infection sets in and a secondary rise occurs [1,2]. Prospective studies have shown that ESR peaks by day four following spinal surgery and in the majority of cases normalizes by two weeks postoperatively [3]. However, monitoring of CRP level was found to be superior to that of ESR for early detection of infections after cervical spine surgery in a series of 51 cases of anterior cervical fusion [4]. A second rise of CRP and ESR or failure to decline is an indicator of potential surgical site infection [5,6]. Limited data is available on the value of Procalcitonin [7].

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Author: Maja Babic

QUESTION 3: Is there a role for the use of serum biomarker for the diagnosis of spinal surgical site infection (SSI)?

RECOMMENDATION: Yes, C-reactive protein (CRP) is a predictable, reliable and economical screening tool for early infectious complications following spine surgery. Erythrocyte sedimentation rate and white blood cell count have nonspecific kinetics that are less helpful in identifying early SSI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 67%, Disagree: 25%, Abstain: 8% (Super Majority, Weak Consensus)

RATIONALE

In a prospective study involving 348 patients who underwent decompression laminectomy, postoperative CRP was helpful in detecting early infectious complications following surgery. As a predictor for early wound infection, the sensitivity, specificity, positive predictive value and negative predictive value for abnormal CRP responses were calculated as 100%, 96.8%, 31.3% and 100%, respectively. Close observation of the surgical site is recommended in patients with abnormal CRP values at day five or seven postoperatively, namely for failure to decline or a secondary rise [1].

Of 149 patients undergoing elective spine surgery, 20 developed infectious SSI complications. Postoperative CRP kinetics were predictable and indicative of early infection where a secondary rise or lack of CRP decrease had a sensitivity, specificity, positive predictive value and negative predictive value of 82%, 48%, 41%, and 86% for infectious complications, respectively [2].

Out of 400 patients undergoing lumbar micro-discectomy over a 15-month period, 9 developed infectious complications related to surgery. CRP values were shown to be a reliable and economic screening tool in identifying the patients at risk with a sensitivity for serial CRP testing (day one and five postoperatively) calculated as 100% with a specificity of 95.8% [3].

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QUESTION 4: Is there a role for molecular techniques such as polymerase chain reaction (PCR) or next-generation sequencing (NGS) for the diagnosis of spinal surgery infection? If so, in which group of patients should this be done?

RECOMMENDATION: It is reasonable to selectively incorporate these diagnostic modalities as an adjunct to standard methodologies where there is a history or high pre-test probability for culture negative infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 71%, Disagree: 14%, Abstain: 15% (Super Majority, Strong Consensus)

RATIONALE

Successful management of periprosthetic joint infections (PJI) is significantly enhanced with a prompt and accurate microbiological diagnosis. Conventional culture methods for diagnosis of PJI can be compromised and complicated by early antibiotic treatment, heterogeneity of surgical sampling, fastidious microorganisms difficult to grow in culture and non-planktonic pathogens utilizing biofilms. Therefore, modern molecular microbiologic methods have naturally been seen as very promising for increasing diagnostic yield in these circumstances. Technologies that have more recently been applied to PJI generally include ribosomal RNA sequencing, species-specific and multiplex PCR and matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS).

Specifically, with respect to spinal and vertebral infections, these varied technologies have demonstrated success in leading to an etiologic diagnosis. These methods have been used to identify a variety of pathogens, including *Staphylococcus spp.* [1–3], *Streptococcus spp* [3,4], *Enterococcus spp.* [4], Enterobacteriaceae [3–5], *Brucella spp.* [6], *Mycobacterium spp.* [2], atypical bacteria (*T. whipplei*) [7], *Mycoplasma spp.*) [8], anaerobes (*Clostridium spp.*) [3], *Fusobacterium spp.*) [4,9] and fungi (*Aspergillus spp.*) [10].

By far, the most experience with these techniques for spinal infections is in the diagnosis of Pott's disease (*Mycobacterium tuberculosis*) [2,6,11–15]. These reports generally demonstrate a high sensitivity and specificity of PCR modalities, though many of these studies have been completed in tuberculosis endemic geographic areas with likely higher inoculum infections and a well-defined pre-test probability.

False positive results from dead or colonizing/contaminating bacteria is a concern with these tests, and studies evaluating the appropriate number of samples to optimize sensitivity and specificity specific to these molecular methods are limited and not specific to spinal infections [16]. Another important concern with molecular techniques for PJI diagnostics is that they do not commonly allow for susceptibility testing to appropriately target antimicrobial therapy. Certain resistance mechanisms, such as methicillin resistance in *S. aureus* [1,17,18] or rifampin resistance in *M. tuberculosis* [12], are reliably expressed if genetically detected. This is not the norm, however, as resistance expression is generally a complex phenotype determined by multiple factors. Care should be taken not to overly rely on non-susceptibility-generating techniques, as they can just as easily lead to long courses of overly-broad therapy, as can no etiologic diagnosis at all, undermining patient safety and important principles of antimicrobial stewardship. In addition, it has been noted that utilizing molecular methods as an adjunct to and in combination with standard culture methodologies often serves to improve overall diagnostic yield [3].

A few studies have attempted to establish test sensitivity and specificity data when compared to routine culture for bone and joint specimens in general [4,15,19–23], however these efforts are limited by lack of a true gold standard diagnostic method for comparison, the variety of testing methodologies clinically employed and non-standardized clinical criteria for utilization of these methods. Predictably, results vary widely, with sensitivities reported between 50–92% and specificities between 65–94% [20]. No studies investigating sensitivity and specificity of these techniques specific only to spinal post-surgical infections have yet been reported. Therefore, an evidence-based evaluation of the appropriate clinical criteria for utilization of these techniques in spinal surgery patients is not currently possible. One study proposed a strategy for routine collection and potential use of molecular diagnostics in PJI [24]. There is no data investigating the cost effectiveness for any diagnostic schema incorporating molecular methods, however given their positive proof-of-concept and the significant clinical impact of spinal post-surgical infections, it seems reasonable to selectively incorporate the use of molecular methods into situations where there is a high pre-test probability for indolent or culture-negative infection as further studies are done to standardize their use.

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QUESTION 5: For which investigations should samples obtained by image-guided biopsy be sent?

RECOMMENDATION: A priority should be placed on obtaining bacterial cultures and pathohistology. In the appropriate epidemiological setting, mycobacterial, fungal and brucellar cultures can be considered.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 0%, Abstain: 7% (Super Majority, Strong Consensus)

RESPONSE

There is limited data available in the literature to help establish clear evidence-based parameters for treatment. However, there are society-based clinical guidelines such as the 2015 Infectious Diseases Society of America (IDSA) clinical practice guidelines for the diagnosis and treatment of native vertebral osteomyelitis in adults, which provide assistance in decision-making. Highlights from this statement recommend the acquisition of image-guided aspiration biopsy in patients with suspected vertebral osteomyelitis when a microbiologic diagnosis for a known associated organism has not been established by blood cultures or serologic tests. Further, they recommend for the addition of fungal, mycobacterial or brucellar cultures on image-guided biopsy and aspiration specimens in patients with suspected vertebral osteomyelitis if epidemiologic, host risk factors or characteristic radiologic clues are present, or if testing to appropriately stored bacterial specimens reveal no growth [1].

There is some data to suggest that standard samples should be sent for both microbiology and pathohistology. Pathologic evaluation is meaningful, particularly in culture negative cases where the presence of leukocytes can indicate pyogenic osteomyelitis, or visualization of granulomas can suggest mycobacterial infection or brucellosis [2]. Pathology can also support ruling out diagnoses like ankylosing spondylitis, hemodialysis-associated spondyloarthropathy or neuropathic Charcot joint deformities [3]. Furthermore, crystal deposits can aid in the diagnosis of pseudogout [4].

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QUESTION 6: How many intraoperative tissue samples should be sent for culture in suspected spinal surgery infection?

RECOMMENDATION: With the currently-available evidence, it is recommended that at least three to five tissue samples be sent for culture in cases of suspected spinal infection. In the setting of instrumentation, we recommend additional techniques, such as vortexing and sonification, to increase the yield of culture samples.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 80%, Disagree: 13%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Turnbull described surgical site infections (SSIs) in spinal surgery in 1953, noting three cases of deep infection of the disc after discectomy as well as significant morbidity that followed [1]. While clinically these cases presented as infection, Turnbull reported them as "presumed" infection because culture of the causative organism was not obtained. Since his work, the incidence of SSI following spine surgery has been studied extensively, with reported incidences ranging from 0.2–15%, varying widely based on underlying pathology and procedure type, with revision procedure, fusion, implantation, and traumatic injury carrying the greatest risk [2–6]. The most common causative culprits are *Staphylococcus* species, including methicillin-resistant *S. aureus* (MRSA) [3,6–9], although less virulent organisms such as *Propionibacterium acnes* can also occur, particularly in revision cases without a definitive preoperative diagnosis of infection [10–12]. Prior to obtaining intraoperative cultures, some suggest computed tomography-guided aspiration, although this practice has been shown to have low sensitivity [13,14].

The evidence for the optimal number of specimens to obtain in cases of suspected spinal infection is sparse. In their study of patients undergoing Cotrel-Dubousset instrumentation, Bemer et al. evaluated cases of *Cutibacterium acnes (C. acnes)* infection, noting that in earlier years of the study one to two samples for culture were obtained, whereas later in their series they had increased that number to four to six samples. Based on their experience and the difficulty in diagnosis of *C. acnes*, these studies recommend that at least four deep tissue samples be taken to facilitate interpretation of the cultures [11].

In the setting of implantation, one major challenge is that peri-implant cultures may not be accurate and it can be difficult for biofilm cultures to grow [15]. In their study of removed spinal implants in the setting of infection, Sampedro et al. report using a technique of vortexing and sonification followed by culturing, which resulted in significantly increased sensitivity compared to simply taking two to nine peri-implant tissue samples [12]. Finally, in a study assessing specimens taken from orthopaedic device revision surgery (5.1% spine cases), the standard procedure was to obtain three to six (mean: four) samples per case, including specimens from the inflammatory membrane around the implant, joint capsule (as applicable) and any macroscopically suspect tissues [16]. In this study, a threshold of at least three positive samples with identical microorganisms was used for diagnosis. The authors note that this definition is strict compared to other studies that use two identical culture-positive specimens for diagnosis and report that their findings would not have differed had they used a lower threshold of two.

It is important to remember that positive cultures may not represent true infection and should be interpreted in the overall context of the individual patient and clinical picture. Gelalis et al. studied bacterial contamination during simple and complex spinal procedures in 40 patients, taking culture swabs during each case, first from the sterile transparent sheet over the operative site at the start of the case, followed by hourly samples from the surgical wound. The authors reported that none of the patients with positive cultures developed clinical signs of infection or required antibiotics, whereas three patients with negative cultures developed postoperative infection [17].

Though there is little guidance in the spine literature, the data in arthroplasty may help to guide future practices. In a study looking at revision hip and knee arthroplasty, Atkins et al. found that the presence of three or more culture-positive specimens was highly predictive of infection (likelihood ratio, 169; sensitivity, 66%; specificity, 99.6%), whereas a single culture-positive specimen was found to have low diagnostic value (likelihood ratio, 0.7; post-test probability of infection, 10.6%) [15]. In their study, the authors determined that five or six samples are required to produce excellent sensitivity and specificity. Similarly, in a study of periprosthetic joint infection caused by MRSA, Parvizi et al. took five cultures in each case [18]. In accordance with the evidence, the Workgroup of the Musculoskeletal Infection Society recommends that three to five culture samples be taken and incubated in an aerobic and anaerobic environment [19].

There is little evidence regarding the optimal number of samples to obtain in the setting of suspected spinal surgery infection. Given the limited data that is available in the spine literature, we conclude that taking at least three to five tissue samples represents current best practice. In the setting of instrumentation, we recommend additional techniques, such as vortexing and sonification, to increase the yield of culture samples.

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2.3. DIAGNOSIS: IMAGING

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QUESTION 1: What is the optimal mode of imaging in the diagnosis of spine infections? If magnetic resonance imaging (MRI) is contraindicated, what imaging modality should be used?

RECOMMENDATION: MRI remains the gold standard for the diagnosis of spinal infection, with sensitivity and specificity above 90%. In the presence of MRI contraindications, consider a combination of modalities, such as computed tomography (CT), positron emission tomography-CT (PET-CT), and single photon emission CT (SPECT)+67Gallium or Gallium-67.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Plain radiography should be the initial exam performed for all patients with non-specific spine or back complaints. In patients with spinal infections, early radiographic findings will occur two weeks to three months after the onset of symptoms. Plain radiographic findings characteristic of a spinal infection include disc space narrowing, end plate irregularity, loss of end plate contour, subchondral defects and/or hypertrophic or sclerotic bone formation. Disc space narrowing has been reported as the most consistent plain radiographic finding occurring in 74% of cases [1]. Late plain radiographic findings include vertebral body collapse, pathologic fractures, segmental kyphotic collapse and/or bony ankylosis. Plain radiography has reported sensitivity of 82% and specificity of 57 to 59% in subjects with pyogenic spondylodiscitis [2,3]. While this modality may not provide the highest level of diagnostic quality, it can give clinicians an understanding of global and focal alignment, deformities associated with infectious processes and mechanical stability [4]. Plain radiographs may also be used for post-treatment surveillance and/or monitoring for potential late deformity or instability associated with these diseases.

CT is an advanced imaging technique that can be utilized for diagnosing spinal infections. It provides higher resolution and multiplanar imaging of the bony architecture. CT findings characteristic of spinal infections can include cystic bony changes, gas within vertebral discs, endplate osteolysis surrounding the vertebral disc and/or paravertebral soft tissue swelling or abscess formation [5–7]. The addition of contrast media during computed tomography can help better delineate the edges of paravertebral abscesses and edematous musculature [5–7]. In cases with neurological deficits or new onset radiculopathy, post-myelogram CT scan can provide excellent detail of the spinal canal and poten-

tial epidural and/or subdural abscesses [8]. In cases where myelogram is performed, it is recommended to analyze the cerebral spinal fluid to rule out meningitis [9]. SPECT is a scintigraphic CT modality that has increased bone contrast resolution, and when combined with technetium or gallium, has high sensitivity and diagnostic accuracy for spinal infections. SPECT with gallium has been shown to be superior to SPECT + technetium and is now the recommended imaging modality for patients with MRI contraindications [10].

MRI remains the gold standard for early and accurate diagnosis of spinal infections [11–20]. MRI has a reported sensitivity of 96%, specificity of 93% and diagnostic accuracy of 94% [18]. MRI has higher accuracy for differentiating degenerative and neoplastic conditions from infections in patients presenting with severe back pain of unknown etiology [11]. While MRI may provide the most detailed information for diagnosing possible infections, it does not reduce the need for tissue biopsy for histological analysis. T1-weighted and T2-weighted sequences should be obtained. The most common MRI findings consistent with spinal infections show decreased vertebral body intensity with poor differentiation between the disc and body on T1-weighted images and increased disc space intensity with marked decreased vertebral body intensity on T2-weighted images [16,18,20]. Utilizing gadolinium contrast can enhance MRI ability to detect and delineate epidural abscesses [21]. All publications consider MRI the gold standard imaging modality for spinal infections and recommend it should be used in all patients without MRI-specific contraindications.

Radionucleotide studies are another modality that is useful for diagnosing spinal infections. These include technetium-99m bone scans, gallium-67 scans, and indium-111 labeled leukocyte scans. Pathologic changes have been shown to appear sooner on radionucleotide studies compared to plain radiography [22–27]. Gallium scans have demonstrated earlier diagnosis of disc-space infections compared to technetium scans and have a reported sensitivity of 89%, specificity of 85% and accuracy of 86% [22,23,28]. Technetium-99m scans have a reported sensitivity of 90%, specificity of 78% and accuracy of 86%.18 When both gallium and technetium scans are performed together, the sensitivity is increased to 90%, specificity 100% and accuracy is 94%.18

Indium-111 scans are known to be sensitive for appendicular skeletal infections, however sensitivity is low in the spine [29–32]. In patients with low-virulence chronic infections, indium-111 scans can provide false-negative results due to white blood cell pooling with any inflammatory process [31]. Indium scans may also result in false-positive results in neoplastic conditions. One important advantage of indium-111 scans is the ability to differentiate non-infectious conditions such as hematoma or seroma in patients with unclear soft tissue etiology. This may be a valuable diagnostic step when investigating possible postoperative infections. Overall, most publications endorsed less utility for radionucleotide studies versus MRI. However, in patients with MRI contraindications, technetium-99m combined with gallium-67 studies is another method that has high sensitivity, specificity and diagnostic accuracy similar to MRI.

There is no single diagnostic test with 100% accuracy for these devastating diseases. A full diagnostic workup includes laboratory studies, blood cultures, imaging and tissue histological analyses. It is generally accepted that plain radiography should be the first imaging study obtained, however, diagnostic sensitivity is low. MRI remains the gold standard with the highest sensitivity, specificity and accuracy compared to other modalities. In the presence of MRI contraindications, clinicians should utilize SPECT+gallium-67 or gallium-67 and technetium-99 combined scans to achieve similar diagnostic accuracy as MRI.

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QUESTION 2: Is there a role for computed tomography (CT) scan with contrast in the diagnosis of spinal infections in patients who cannot undergo magnetic resonance imaging (MRI)?

RECOMMENDATION: Although evidence is limited for the routine use of CT scan with contrast, there is a role for it to be used in the presence of spine infection where MRI is contraindicated or when other advanced imaging is not available

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Although there is growing evidence of the safety of MRI in the presence of implanted metallic devices [1], obtaining such a study may not always be possible. CT with either extradural or intravenous contrast can be used to identify spine infections.

Prior to the wide adoption of MRI, CT myelography was commonly used to diagnose extradural compressive pathology such as epidural abscesses [2]. The use of this invasive investigation in the setting of postoperative spine epidural abscess has not been studied. However, it can be assumed that the accuracy will be lower due to metal artefact [3].

The role of CT with intravenous contrast in the postoperative setting is unclear and has not been directly studied. CT is most useful in identifying implant and bony related complications such as implant loosening, endplate erosion and destruction. The addition of contrast provides information on paraspinal soft tissue involvement, phlegmon or abscesses albeit with lower sensitivity and specificity when compared to MRI [4].

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QUESTION 3: Is there a role for nuclear imaging (e.g., positron emission tomography scan (PET)) in the diagnosis of spinal infections?

RECOMMENDATION: PET scan, preferably PET-computed tomography (PET-CT), can be used as an adjunct to magnetic resonance imaging (MRI) to diagnose spinal infections when an MRI cannot be performed or is inconclusive.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

At the present time, MRI is the imaging test of choice for diagnosing spondylodiscitis (SD). This study should be performed when SD is suspected to avoid the morbidity and mortality associated with a delay in diagnosis. MRI is a favored choice as part of an infectious work up due to its lack of ionizing radiation, multi-planar capability, superior soft tissue contrast and ability to evaluate the neural structures. It has a sensitivity and specificity of 97% and 93% respectively. Ultimately, its accuracy in diagnosing SD is 94% [1–3]. A typical protocol should include T1- and T2-weighted sequences with gadolinium. T2 and post-gadolinium T1-weighted sequences should also be performed with fat suppression to increase the sensitivity of identifying pathology [4,5]. Furthermore, MRI allows for the evaluation of bone marrow edema and disc space inflammation, as well as paraspinal and epidural soft tissue involvement. Gadolinium is helpful in differentiating phlegmonous changes versus abscess formation.

Fluorine-18-fluorodeoxyglucose (18F-FDG) is the radionuclide-imaging test that can be a useful compliment to MRI. The role of 18F-FDG in the diagnosis of SD has been extensively investigated [6–13]. It has shown acceptable levels of sensitivity and specificity and is useful when MRI cannot be performed or is inconclusive. In addition to its value for diagnosing spondylodiscitis, 18F-FDG can be utilized to monitor response to treatment. Gallium-67-SPECT/CT is an acceptable alternative when 18F-FDG is not available [14].

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QUESTION 4: How can postoperative infections be distinguished from normal postoperative changes on magnetic resonance imaging (MRI)?

RECOMMENDATION: The presence of an abscess in the back muscles or posterior site, confirmed by gadolinium enhancement, is the most frequently-reported change on MRI of patients with surgical site infection (SSI). The presence of a collection of fluid outside the head of the pedicle screws is another sign of SSI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 71%, Disagree: 8%, Abstain: 21% (Super Majority, Strong Consensus)

RATIONALE

A search was conducted using the MeSH terms "spine AND MRI AND surgical site infection." The initial search yielded 149 references, and after screening, 13 abstracts remained. However, only three studies assessed the use of MRI for postoperative spine infections and were found eligible.

Kanayama et al. retrospectively used MRI in 20 patients with surgical site infections after instrumented spinal surgery [1]. In their series they considered two markers for diagnosing SSI: (1) the presence or absence of osteomyelitis at the instrumented vertebra and (2) the presence or absence of intervertebral abscess. All 20 patients had a confirmed SSI, but in 7 MRIs it was considered negative. The study mainly aimed to assess the utility of MRI to confirm the severity of the infection. Using the above-mentioned criteria, they tried to predict the need for implant removal. However, MRI was not evaluated as a diagnostic tool for assessing the presence or absence of infection.

Kim et al. reviewed 43 patients with MRI after SSI [2]. First, they divided their infections on an anatomical basis, assessing if it affected only the posterior region (31 cases), only the anterior area or both posterior and anterior regions [2]. In addition, they looked for abscess in different spinal locations (posterior epidural space, laminectomy site, back muscles, subcutaneous fat layer, paravertebral space, psoas muscle and anterior epidural space). They also evaluated the presence of osteomyelitis of the vertebral body and discitis. The most frequent findings were abscesses in the back muscles in 40 patients (93%), abscesses in the laminectomy site in 29 (67.4%) and in the subcutaneous fat layer in 27 (62.8%). All abscesses were identified by the presence of peripheral rim or diffused enhancement of adjacent soft tissue after administration of intravenous gadolinium.

They did not compare their findings with those of patients without confirmed SSI. The authors concluded that for diagnosing infection, the posterior surgical field was more important than the vertebral body or the disc area. This conclusion supports the findings of the previous study by Kanayama, in which seven patients with SSIs did not show involvement of the vertebral body or the disc area.

Finally, Kimura et al. published a comparative study on postoperative MRI including 17 patients with a deep SSI and 64 non-SSI controls who had an MRI examination within 4 weeks after surgery [3]. Their investigation focused on the "pedicle screw fluid sign" (PS fluid sign) and did not search for other signs of infection. The PS fluid sign refers to the collection of fluid outside the head of a pedicle screw, suggesting the presence of an abscess on axial MRI scans. The authors observed that fluid collections medial to the pedicle screw head are not infrequent. They considered that when the collection expands outside the head of the screw into the paravertebral

muscles, it is likely to be an abscess. In their view, artifacts have little effect on the area outside the screw head, compared with the inside. In their study, this sign was positive in 15 of 17 deep SSI infections and only in 7 of 64 patients without infection. Sensitivity was 88.2%, specificity 89.1%, positive predictive value 68.1% and negative predictive value 96.6%.

In conclusion, abscesses in the back muscles, laminectomy site and subcutaneous fat layer, after administration of gadolinium were the most common findings related with surgical site infection. In addition, the PS fluid sign had a sensitivity of 88.2% and specificity of 89.1%.

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Treatment

3.1. TREATMENT: GENERAL PRINCIPLES

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QUESTION 1: Can a non-surgical approach be used to treat postoperative spine infections? If so, what factors predict a successful outcome?

RECOMMENDATION: Postoperative spine infections should be treated with irrigation and debridement (with or without implant removal) followed by appropriate antibiotic therapy. Antibiotic suppression without surgical intervention should be attempted in cases where the patient is not a surgical candidate, or in attempt to achieve spinal fusion prior to implant removal.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 80%, Disagree: 7%, Abstain: 13% (Super Majority, Strong Consensus)

RATIONALE

Postoperative surgical site infections are a major complication that occur between 1 and 12% of all spinal surgeries [1–3]. Treatment varies based on general location in relation to superficial, or deep to the muscular fascia, and the time from initial surgery, with early infections occurring before 90 days and late infections occurring after 90 days.

In the case of superficial wound infections, local debridement, healing by secondary intention and a short course of antibiotics is usually sufficient [4]. Deep surgical site infections, on the other hand, require aggressive irrigation and debridement with or without implant removal. The retention of hardware predominantly depends on if the infection is early or late. Several studies have demonstrated that hardware can be retained successfully following aggressive irrigation and debridement in the setting of early infection, except in cases where the implants are loose or there is bony involvement [5–9]. Optimal treatment of delayed infections is aggressive irrigation and debridement with implant removal [10–12]. In the cases where spinal fusion has been achieved, implant removal is routinely performed. However, in cases of fusion failure or pseudoarthrosis, surgical options include aggressive debridement and irrigation with attempted implant retention, implant removal with primary or delayed reimplantation or implant removal without reimplantation [6,13–16].

Antibiotic suppression without surgical intervention is attempted in cases where the patient is not a surgical candidate, or in an attempt to achieve spinal fusion prior to implant removal.

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QUESTION 2: When should patients with suspected infections of the spine be referred to an infectious disease department?

RECOMMENDATION: There is no data on the timing or need for a referral to an infectious disease department. We support a multidisciplinary approach to managing clinical spine infections.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Only one paper has addressed the collaboration with an infectious disease-specialized team in order to improve outcomes for patients with spinal surgical site infections (SSIs). The paper is a retrospective study reporting on 40 patients, none of whom needed implant removal [1]. The paper didn't report on the exact timing when collaboration started, but reported three main advantages related with this collaboration:

1. Efficient detection of auxiliary bacteria (reached 88%)
2. Early treatment with antibiotics
3. Appropriate duration of administration of antibiotics

There were no other papers which discussed this issue, and all subsequent searches on related articles yielded no more information on the matter.

From a theoretical point of view, referral, or at least counselling by an infectious diseases specialist, might have some advantages. Antibiotic treatments are more complex today and only specialists are adequately up-to-date on the issue. The appropriate treatment choice might be difficult in patients with allergies, multi-resistant smears or simply a low tolerance for the medication. Adjusting the choice of antibiotic, taking into account side effects and tolerance, will very likely improve compliance, which is paramount in reaching a successful treatment outcome.

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QUESTION 3: Which patients with vertebral osteomyelitis (VO) are suitable for outpatient management? Does any criteria exist to aid in this decision-making?

RECOMMENDATION: There are no studies aiming to identify which patients diagnosed with VO can be treated on an outpatient basis.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 7%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

VO, also known as spondylodiscitis, describes an infection of the vertebrae and intervertebral disc. By comparison, discitis describes infection limited to the intervertebral disc, however there are many who consider discitis and VO to be different stages of the same disease process. VO can arise from hematogenous seeding, contiguous spread from infection in adjacent soft tissues or direct inoculation during spinal surgery or procedures (i.e., epidural). Management of native vertebral osteomyelitis (NVO) depends on the location of the infection, disease progression and the patient's general condition including age and comorbidities.

Conservative treatment is reasonable in the early stages with no or minor neurologic deficits or in the case of severe comorbidities. However, in cases of doubt, surgical treatment should be considered. Both options require a concomitant antimicrobial therapy, initially applied intravenously and administered orally thereafter [1]. To date, there is no consistent data from randomized controlled trials to guide the optimal duration and appropriate route of antibiotic therapy. Although the optimal duration of antibiotic therapy remains controversial, it should never undercut six weeks [2]. Recent Infectious Diseases Society of America (IDSA) guidelines for the diagnosis and treatment of NVO in adults include evidence and opinion-based recommendations for the management of patients with NVO treated with antimicrobial therapy, with or without surgical intervention, but do not address the issue of which patients affected by NVO can be treated on an outpatient basis [3,4]. The extent of pursuing spinal biopsies to determine etiology, antimicrobial therapy, response to treatment and preference for surgical techniques and timing all vary widely in clinical practice with heterogeneous studies limiting comparisons. Surgery, rather than conservative approaches, is being proposed as the default management choice because in carefully-selected patients it can offer faster reduction in pain scores and improved quality of life [5–9]. Due to a

heterogeneous and often comorbid patient population and the wide variety of treatment options, no generally applicable guidelines for VO exist and management remains a challenge.

The goals of treatment include establishing a diagnosis and identifying the pathogen, eradicating the infection, preventing or minimizing neurologic involvement, maintaining spinal stability and providing an adequate nutritional state to combat infection. Often, this can be accomplished with non-operative approaches.

The mainstay treatment of pyogenic infections of the spine remains antibiotic therapy and immobilization with a proper orthosis. If nonsurgical treatment fails, however, surgical intervention may be required. Surgery is indicated in the following circumstances: to obtain a bacteriologic diagnosis when closed biopsy is negative or deemed unsafe, when a clinically significant abscess is present (spiking temperatures and evidence of sepsis), in cases of refractory to prolonged non-operative treatment where the sedimentation rate remains high or pain persists, in cases of spinal cord compression causing a neurologic deficit and in cases of substantial deformity or vertebral body destruction, especially in the cervical spine. Alton et al. reported that 75% of patients with an epidural abscess in the cervical spine who underwent medical management failed and that medical management failure was associated with a significantly increased risk of neurologic injury [10]. Patel et al. reported on 128 patients with an epidural abscess and found that 41% failed medical management. However, there were significant predictors of medical failure [11]. Four key predictors were identified, including diabetes mellitus, C-reactive protein (CRP) greater than 115, white blood cell count greater than 12.5 and positive blood culture. Patients with none of the aforementioned parameters only failed 8.3% of the time. Those with one parameter failed 35.4% of the time, those with two parameters failed 40.2% of the time and patients with three or more parameters failed 76.9% of the time.

Once the antibiotic is prescribed by oral route, if the patient is stable, the treatment could be administered in an outpatient setting. Several studies described a successful switch to oral antibiotics after 10 days, using oral agents with a high bio-availability and tissue penetration (i.e., fluorquinolones, rifampin, fusidic acid and clindamycin) [12–15]. A retrospective analysis of all patients diagnosed with NVO, at the University Hospital of Basel, Switzerland, concluded that switching to an oral antibiotic regimen after two weeks of intravenous treatment may be safe, if CRP has decreased compared to baseline CRP and epidural or paravertebral abscesses of significant size have been drained [16]. Importantly, these results do not extend to patients with endocarditis, surgical site infection, and/or vertebral implants. Also, positive blood cultures, neurological abnormalities and staphylococcal infections (compared with negative microbiology) are associated with longer intravenous courses [17].

Outpatient parenteral antibiotic therapy (OPAT) has become an option allowing for early discharge of hospitalized patients who have infections without a reliable oral alternative and requires lengthy antibiotic therapy. It provides numerous benefits, some of the most remarkable being that OPAT permits early discharge and reduces costs, avoids hospitalization trauma in children or immobilization syndrome in the elderly and reduces nosocomial infections by multidrug resistant organisms [17]. OPAT also allows for self-administration of antibiotics using elastomeric pumps [18,19]. Different retrospective studies and case series have reviewed the experience with OPAT in several countries [17,19–27]. β-Lactam antibiotics are commonly used in OPAT with higher treatment success among those treated with ceftriaxone and ertapenem, while oxacillin was associated with a higher rate of antimicrobial discontinuation because of antimicrobial-related complications [17,20,26]. Other alternatives are teicoplanin, telavancin or daptomycin in the case of gram-positive infections [17,25,28]. All this data regarding OPAT confirms that infection management in an outpatient setting is safe, clinically efficacious, and acceptable for treating a wide range of infections with high levels of patient satisfaction and substantial cost savings. Therefore, OPAT could be considered an effective alternative for appropriately selected elderly patients with vertebral osteomyelitis.

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QUESTION 4: What is the optimal treatment of spinal infections caused by *Propionibacterium acnes* (*P. acnes*)?

RECOMMENDATION: When possible, patients should undergo complete removal of implants after *Cutibacterium acnes* (*C. acnes*) (formerly *P. acnes*) infection, especially in the setting of latent infection. Antibiotic regimens typically involve specific parenteral antibiotics for a period of greater than two weeks, with the most common antibiotic duration being six weeks of multiple parenteral and/or oral agents. However, the duration of antibiotic treatment is highly variable. It is unclear in which setting patients may be successfully treated with antibiotic therapy alone and instrumentation may be retained. Penicillin is currently the standard of care, but other non beta-lactam antibiotics should be considered based on the susceptibility profile.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 73%, Disagree: 7%, Abstain: 20% (Super Majority, Strong Consensus)

RATIONALE

P. acnes is an anaerobic, gram-positive bacillus existing as normal flora of the skin and sebaceous glands and was originally considered a common contaminant of blood cultures as well as an uncommon cause of brain, pulmonary and dental infections [1]. *C. acnes* infections are commonly thought to originate from patient skin approximation with surgical sites, are frequently poly-microbial, require an extended incubation period in culture media for diagnosis and form a resistant biofilm, making treatment with antibiotics alone difficult [2–4].

P. acnes infection of the spine was first reported as an etiology of spine infection by Serushan et al. in 1982 [5]. The patient presented with osteomyelitis of the cervical spine and was treated with 40 days of intravenous penicillin with resolution of his fever and neck pain. *C. acnes* has subsequently been implicated in vertebral osteomyelitis and discitis and may present with insidious onset of back pain, fever and/or neurologic symptoms, with treatment typically involving administration of parenteral antibiotics. Additional debridement or percutaneous drainage of abscesses occurs in rare cases [6–8]. Duration of antibiotics ranged from 2-28 weeks in one series, and typically involved multiple agents due to the frequency of co-infection with other pathogens including *Staphylococcus,* Lactobacillus and Enterococcus species [9].

Tsai et al. reported on successful treatment of two cases of *C. acnes* osteomyelitis of the cervical spine with anterior debridement, decompression and fusion with autograft and treatment with a combination of oral and parenteral antibiotics for 6-16 weeks [10]. Overall, the decision to treat *C. acnes* vertebral osteomyelitis and discitis with surgery, antibiotics or a combination of these approaches has been made on a case-by-case basis. No well-defined, widely-applicable treatment regimen was identified in the literature.

C. acnes also frequently presents as a delayed infection after spinal instrumentation, which has been attributed to its low virulence and slow growth rate, and is common in instrumented pediatric scoliosis surgery [4,11–17]. Viola et al. reported a series of eight patients with delayed infection, one of which had *C. acnes* infection and was treated with irrigation and debridement, removal of instrumentation and six weeks of cefotetan with good results and no loss of balance or alignment at midterm follow-up. Of 23 patients with delayed infections after posterior TSRH instrumentation, Richards and Emara found that the causative agent in delayed infections was *C. acnes* in 12 (52.1%). Patients underwent removal of instrumentation with either primary or delayed closure and parenteral antibiotics (two to five days) followed by a course of oral antibiotics for an additional two to four weeks [18]. Tribus reported on a delayed infection with *Staphylococcus epidermidis* and *C. acnes* resulting in laminar erosions seven years after TSRH instrumentation. The patient was treated with removal of instrumentation and seven weeks of intravenous vancomycin and oral rifampin with resolution of pain and infection [12]. In cases of late implant infections, successful treatment typically involved implant removal and greater than two weeks of a combination of parenteral and oral antibiotics.

In the largest single study evaluating treatment of *C. acnes* infection after Cotrel-Dubousset instrumentation, Bemer et al. conducted a retrospective study investigating various treatment regimens including complete or partial implant removal, implant replacement and maintenance of implants with irrigation and debridement, both with and without antibiotics. Patients who underwent partial removal with antibiotic monotherapy or absence of antibiotic therapy were more likely to develop a secondary infection. Ultimately, wide variation in treatment regimens prevented more mean-

ingful analysis of the results, though the authors concluded that complete removal of implants should be performed when possible and antibiotics should be tailored to the sensitivities of the specific organism and given for a duration of three to six months or less than three months when following total implant removal [19]. In another large case series of surgical site infection (SSI) after spine surgery, Maruo and Berven listed *C. acnes* infection as an independent risk factor for treatment failure ($p = 0.042$) [4]. Though they did not comment on the specific treatment strategies utilized for patients with *C. acnes* SSI, they note that 7 of 12 patients (58%) with late infection treated with implant retention and antibiotics required subsequent implant removal.

Due to the variation in treatment strategies for *Propionibacterium acnes* infections of the spine and the lack of prospective trials evaluating optimal antibiotic regimen, the optimal treatment of spinal infections with *C. acnes* is indeterminate. However, given reports of numerous successful treatment strategies in the literature, complete removal of implants when applicable followed by an extended course of parenteral antibiotics results in overall high cure rates for *C. acnes* infections of the spine.

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3.2. TREATMENT: ANTIBIOTICS

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QUESTION 1: Is there a role for oral antibiotics in the treatment of early postoperative spine infections?

RECOMMENDATION: There may be a role for highly bioavailable oral antibiotics in the treatment of early postoperative spine infection in select circumstances.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Broad-spectrum intravenous (IV) antibiotics may be indicated prior to identification of the infecting organism in patients with early postoperative infections while waiting for surgical intervention, or for patients who are medically unstable and cannot undergo surgery [1]. Other than the latter cases, there is no role for oral antibiotics alone in the treatment of patients with acute postoperative spine infections. Patients with established postoperative infections of the spine require surgical intervention.

The administration of antibiotics may potentially adversely affect the outcome of treatment of these patients by interfering with isolation of the infecting organism. Antibiotic therapy should be withheld in patients with suspected spine infection, as the yield for biopsy to isolate the infecting organism is reduced when the antibiotic is administered. In a study by Cornett et al., the yield for biopsy culture dropped from 80% for those who did not receive antibiotics to 48% for those who did [1]. Another study of 87 patients, however, demonstrated that the yield for biopsy of spondylodiscitis did not significantly decrease with prior treatment of antibiotics [2]. Despite this, it is still recommended that antibiotics be withheld when possible. If antibiotics are to be administered, biopsy is still indi-

cated to isolate the infecting organism and allow for optimal treatment of the patient.

In a large case series of 1,980 patients, 74 infections were diagnosed [3]. The treatment algorithm consisted of six weeks of IV antibiotics if the patient was not fused. If the patient was fused, *Staphylococcus aureus* and gram-negative infections were treated with six weeks of IV antibiotics followed by six weeks of oral antibiotics with implant removal. In patients with propionibacteria and coagulase-negative *Staphylococcus*, four weeks of oral antibiotics were given. Oral antibiotics were not recommended as an initial treatment. Other studies have demonstrated the benefit of oral antibiotics as suppression therapy after treatment with surgical debridement and a course of IV antibiotics [4,5].

Multiple other studies have demonstrated the benefit of surgical debridement and IV antibiotics for infection [6]. In a consecutive case series of 2,391 patients, 46 cases of wound infection were identified and all treated with surgical debridement [7]. One series of 111 patients identified eight patients with postoperative infections after posterior lumbar interbody fusion [8]. All were treated with irrigation and debridement followed by four to six weeks of intravenous antibiotics followed by another six to nine weeks of oral antibiotics.

Multiple case series and expert opinion studies recommend avoiding oral antibiotics in suspected postoperative infection until culture samples are taken for better diagnosis and accurate treatment of these patients [9]. The majority of patients with established postoperative infection require surgical debridement.

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QUESTION 2: Is there a role for the use of oral antibiotic in treatment of acute and chronic spinal infections?

RECOMMENDATION: There may be a role for highly bioavailable oral antibiotics in the treatment of acute and chronic spine infection in select circumstances.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Vertebral osteomyelitis

In vertebral osteomyelitis (spondylodiscitis) without an implant, experts recommend a treatment duration of 6 to 12 weeks [1]. However, a retrospective study over 10 years by Roblot et al. found no difference in relapse rate comparing 6 and 12 weeks of treatment [2]. An open label, non-inferiority, randomized, controlled trial by Bernard et al. firstly showed that 6 weeks was not inferior to 12 weeks. In both groups, intravenous treatment was only given for a median time of 14 to 15 days and was followed by an oral fluoroquinolone and rifampin combination or aminopenicillin (both regimens with high oral bioavailability) [3]. The authors could not see a difference in the proportion of treatment failure between patients given intravenous treatment for more than one week and those for less than one week.

Postsurgical infection with an implant

There are many studies in this field regarding optimal treatment duration and agents in spinal implant-associated infections, but they are all retrospective with low levels of evidence. There are no up-to-date prospective and/or randomized studies published investigating the optimal duration of antibiotic treatment and the role of oral antibiotics in implant-associated spinal infections.

Most studies demonstrated successful treatment of spinal implant-associated infections with a total duration of six weeks [4–6]. If implants are not removed, reported durations of treatment are up to 12 weeks with intravenous treatment for 6 weeks, followed by oral antibiotic treatment for another 6 weeks [7,8].

Yet, regarding duration of intravenous treatment, there are no clear recommendations. Some studies treat intravenously for a prolonged time for up to four [8–10] or six weeks [4,11–13]. But there are also retrospective studies in which intravenous treatment was given for two weeks or less followed by oral antibiotics with good oral bioavailability [14]. Billieres et al. did a multivariate analysis on risk factors for relapse of infection and did not find an association with duration of total or intravenous antibiotic treatment [14]. Another study by Kowalsky et al. also concluded that duration of

intravenous treatment is no risk factor for neither acute nor chronic infections [15].

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QUESTION 3: Is there a role for chronic antibiotic suppression after treating patients with retained infected spinal hardware?

RECOMMENDATION: The use of chronic antibiotic suppression (CAS) has not been clearly investigated until now. However, it can be an option for patients whose implants cannot be removed or who refuse further surgeries because of comorbidities.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 93%, Disagree: 0%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Only one study has compared patients receiving CAS [1]. They found that 5 out of 22 patients with CAS had treatment failure, compared with 5 out of 6 in the control group. The definition they used for treatment failure was described as the need for an unanticipated debridement or a clinician's decision to give a second course of antibiotics. Suppressive antibiotics were given for a median time of 303 days (IQR 147 to 672) to patients with early onset infection and 410 days (IQR 61 to 667) to patients with late onset infection. Data on treatment failure was reported only for early onset infection patients. It could be argued that patients already under CAS would not have been eligible for a second course of antibiotic treatment and this could partly increase the rates of treatment failure on the group without CAS, biasing the study results.

Other studies reporting on antibiotic treatments show large variations in the duration of treatment. Miyazaki et al. reported a mean duration of oral treatment of 336 days, ranging from 89 to 1,673 days [2]. Their study focused on multi-resistant surgical site infection treated with implant retention. Maruo et al. reported an average duration of antibiotic treatment of 255.8 days with a standard deviation of 283.4 days [3]. All these reports show a huge variation in the length of antibiotic treatment, with a select group of patients in each study receiving CAS. Decision for prolonged CAS was made at the clinician's discretion and based on the patient's symptoms, so there is no particular setting in which it would be possible to offer a sound recommendation. Besides the mentioned paper by Kowalski, there are no reports comparing CAS with other treatment regimes.

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QUESTION 4: Is there a role for combination antibiotics (i.e., dual or triple) in treating patients with surgical site infection (SSI) following spinal surgery?

RECOMMENDATION: There is insufficient evidence to recommend the routine use of combination antibiotics in the setting of postoperative spine infections. However, there may be a role for combination antibiotics in certain circumstances related to specific pathogens.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 87%, Disagree: 13%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

The incidence of postoperative spine infection has been reported as between 0.7 and 16%, with higher rates noted in procedures with hardware implantation [1,2]. The most common organisms isolated are *Staphylococcus aureus*, *Staphylococcus epidermidis*, methicillin-resistant *S. aureus* and *Enterococcus*. Up to 20 to 30% of infections are noted to be poly-microbial [3,4].

Antibiotic treatment is directed at the isolated micro-organism/s and usually only a single anti-microbial agent is used. There are a few reports of dual antibiotic therapy with rifampin, the most common additive agent [3,5]. Rifampin is chosen due to its ability to penetrate biofilms associated with implant-related infections [6]. Evidence from a mouse model has shown that the addition of rifampin to vancomycin led to an increase in bacterial death, but no change in the final outcome from the SSI [7]. There are no clinical studies comparing the use of single to multi-agent antibiotic therapy for postoperative spine infections.

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QUESTION 5: How long should antibiotics be administered after surgical debridement for an acute postsurgical spinal infection?

RECOMMENDATION: For vertebral osteomyelitis: Initial intravenous treatment for one to two weeks, followed by an oral treatment of four to five weeks to reach a total treatment duration of six weeks.

For deep surgical site infections: There is limited knowledge about the ideal duration of antibiotic treatment and which intravenous and/or oral agents should be given. As extrapolated from studies in periprosthetic joint infections (PJIs) and retrospective studies in spine infections, 12 weeks of antibiotic treatment can be recommended in cases with early infection and implant retention, six weeks if the implant is removed and prolonged suppressive treatment in delayed infections without removal of the implant.

LEVEL OF EVIDENCE: Moderate for vertebral osteomyelitis. Limited for surgical site infections after spine surgery

DELEGATE VOTE: Agree: 80%, Disagree: 13%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Vertebral Osteomyelitis

In vertebral osteomyelitis (spondylodiscitis) without an implant, experts recommend a treatment duration of 6 to 12 weeks [1]. However, a retrospective study over 10 years by Roblot et al. [2] found no difference in relapse rate between 6 and 12 weeks of treatment [2]. An open label, non-inferiority, randomized, controlled trial by Bernard et al. first showed that 6 weeks was not inferior to 12 weeks. In both groups, intravenous treatment was only given for a median time of 14 to 15 days followed by an oral fluoroquinolone and rifampin combination or aminopenicillin (both regimens with high oral bioavailability) [3]. The authors could not see a difference in the proportion of treatment failure between patients given intravenous treatment for more than one week and those for less than one week.

Postsurgical infection with an implant

There are many studies in this field regarding optimal treatment duration and agents in spinal implant-associated infections, but they are all retrospective with low levels of evidence. There are no up-to-date prospective and/or randomized studies published investigating the optimal duration of antibiotic treatment and the role of oral antibiotics in implant-associated spinal infections.

Most studies demonstrated successful treatment of spinal implant-associated infections with a total duration of six weeks [4–6]. If implants are not removed, reported durations of treatment are up to 12 weeks with intravenous treatment for six weeks, followed by oral antibiotic treatment for another six weeks [7,8].

Yet, regarding duration of intravenous treatment, there are no clear recommendations. Some studies treat intravenously for a prolonged time for up to four [8–10] or six weeks [4,11–13]. But there are also retrospective studies in which intravenous treatment was given for two weeks or less followed by oral antibiotics with good oral bioavailability [14]. Billieres et al. did a multivariate analysis on risk factors for relapse of infection and did not find an association with duration of total or intravenous antibiotic treatment [14]. Another study by Kowalsky et al. also concluded that duration of intravenous treatment is not a risk factor for acute chronic infections [15].

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QUESTION 6: How long should antibiotics be continued when spinal wounds are left to heal by secondary intention?

RECOMMENDATION: Only standard perioperative antibiotic prophylaxis is recommended.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 0%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Following spine surgery, surgical wounds are normally closed via primary intention where all tissue is fastened closed with sutures, staples, glue or some other form of closure material. In rare cases, however, wounds are left to close naturally via secondary intention. Normally, this is done in cases where the risk of persistence of infection is high or when a large gap in soft tissue exists as a result of tissue loss.

Antibiotic prophylaxis has been shown to be useful in preventing infection following spine surgery. However, no specific agent or schedule has been identified as superior over any other [1].

In a randomized, blinded, controlled study, Gupta et al. found that topical antibiotics, specifically sucralfate, increased wound healing in patients at four weeks following hemorrhoidectomy left to heal via secondary intention when compared to placebo (78% compared to 52%) [2]. In contrast, Doung et al. found that the use of trimethoprim-sulfamethoxazole in pediatric skin abscess treatment compared to placebo did not significantly affect the recurrence of new lesions in the long term [3].

A systematic review by Norman et al. found that no robust evidence exists on the relative effectiveness of any antibiotic preparation in cases where surgical wounds have been left to heal by secondary intention [4]. There is no high-level evidence directly related to spine surgery for this topic. In general, if there is hardware present, patients often should receive at least six weeks of intravenous antibiotics and continued suppressive antibiotics until the wound heals.

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QUESTION 7: What is the optimal duration of antibiotic treatment following spine infection in patients within whom hardware is retained? Is the antibiotic treatment different for those with spine infection without hardware?

RECOMMENDATION: There are no case-control studies allowing for an evidence-based recommendation on the optimal length of antibiotic treatment following spine infections in the presence of retained hardware. The most commonly implemented antibiotic regime is three months. However, duration of treatment was highly variable among all studies. Patients with non-instrumented surgeries did well with a shorter course of antibiotics.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 93%, Disagree: 7%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

After searching PubMed, CINAHL and Embase (with MeSH terms "surgical site infection," "spine" and "antibiotic") and reviewing 381 abstracts, a final 14 studies included treatment of spinal surgical site infection (SSI) with retained implants (including data on antibiotic treatment regimens) [1–14]. There were no studies analyzing or comparing different antibiotic regimes. Most of these studies were retrospective in nature, however one study was a prospective observational study. There were no studies comparing different antibiotic treatment regimens. There was also a wide variation in the duration of treatment among the studies ranging from 42 to 597 days in 1 study, and ranging between 89 and 1,673 days in a separate study [9,11]. These variations were usually related to treatment failure or poor control of the infection. Of 14 studies, 7 reported mean antibiotic treatments of 12 weeks or 3 months [3–6,10,13,14]. All but three studies reported on time of intravenous (IV) and oral antibiotics. The most reported mean time for IV antibiotic administration was an average of four to eight weeks in eight studies. One study reported on 81 SSIs, of which 39 were treated with suppressive antimicrobial therapy [2]. At final two-year follow-up, seven patients were still under antibiotic treatment.

Three studies reported data on patients with early and late infection [2,5,10]. Also, there were significant variations regarding the onset of infection. Some studies only reported ranges and gave no mean or median values. Of the nine studies with available mean data, mean time to onset of infection was 103.2 days. Removing an outlier with 778 days for late infection, mean time to onset of infection was 18.98 days (range of mean values was 2.9 to 54)

There was only one retrospective study analyzing the antibiotic treatment regimen in a series of 74 patients, all with implant removal (IR) [15]. Patients had a median duration of IV antibiotics of four weeks and an additional five weeks of oral antibiotic treatment. There were no comparative studies regarding different antibiotic regimen.

Regarding IR, there were two very different settings in which implants had to be removed. Of 729 SSI cases recorded in the 15 studies, implants were removed in 195 patients (26.74%). In 114 cases (15.6%), IR was performed as part of SSI treatment during the first debridement procedure. In the remaining 81 cases (11.11%), IR was performed because of treatment failure after several debridement procedures. The fact that IR can be split into two differentiated groups makes it more difficult to compare treatment regimes. Usually, when IR was performed as the initial treatment, antibiotic regimens tended to be shorter [15]. On the other hand, when IR was performed because of treatment failure, antibiotic treatments were longer.

With regards to non-instrumented spine surgeries, Maruo et al. compared 59 non-instrumented infections with 166 instrumented cases [8]. They reported longer antibiotic treatment for instrumented cases (mean 40 days IV vs. 25.4 in non-instrumented and mean 255 days oral vs. 42). Only 10% of the non-instrumented cases needed more than one debridement compared to 28% for instrumented spine procedures. Of the non-instrumented spine surgeries, 20% were successfully treated without surgical debridement compared to only 6% of instrumented spine procedures.

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QUESTION 8: What tests should be used to monitor response to antibiotic treatment in patients with spine infection?

RECOMMENDATION: Serum C-reactive protein (CRP) levels are closely related to clinical response in spine infections and are therefore the preferred marker in monitoring the therapeutic course.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 7%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

In two large retrospective studies including 363 patients, criteria for discontinuation of treatment included CRP normalization in addition to resolution of clinical symptoms [1,2]. A weekly decrease of CRP by 50% has been suggested as a therapeutic response in the retrospective study population [3].

Lack of normalization of serum CRP levels is a predictor of treatment failure and warrants additional evaluation, as demonstrated both by a retrospective cohort including 79 patients and a prospective study including 21 patients followed for postsurgical wound infections of the spine [4–5].

Moreover, in a retrospective analysis of 61 patients treated for bacterial spondylodiscitis, the only predictor for de-escalating intravenous therapy to highly bioavailable oral agents was a CRP decrease by week 2 of therapy [6].

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QUESTION 9: Which is the best alternative antimicrobial therapy for fluoroquinolone-resistant gram-negative acute post-surgical infection in spinal surgery?

RECOMMENDATION: The choice of antimicrobial therapy should be based on the pathogen and the susceptibility profile.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 7%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

Currently, over 30% of all spinal surgical site infections (SSIs) are secondary to gram-negative bacteria (GNB). Focusing on acute post-surgical infection of spinal surgery, there is no published experience regarding the best therapeutic strategies in case infection by GNB resistant to quinolones. Thus, the treatment criteria used in these cases are the same as those used in the case of fluoroquinolone-resistant GNB periprosthetic join infections (PJIs). The importance of using fluoroquinolones in acute PJIs due to gram-negative bacilli has been demonstrated, but limited antimicrobial agents are available in the case of implant-associated infections caused by fluoroquinolone-resistant GNB [1–3].

The most commonly used antibiotics in the event of fluoroquinolone resistance are β-lactams and carbapenems with or without anti-pseudomonal activity [4]. Grossi et al. described the outcome of 76 GNB-PJIs managed with a curative intent and in their experience, intravenous β-lactams throughout treatment duration (median 90 days) results in an effective alternative to fluoroquinolones [5].

Therapeutic alternatives to β-lactams have been poorly assessed. Cotrimoxazole, which can be switched to oral therapy, has been successfully used in some of these cases [1–6]. Other possible alternatives are the "recovery" of the use of less conventional antibiotics, such as colistin and fosfomycin [7–9]. Colistin shows good spread in bacterial biofilm and a synergistic effect when combined with other antibiotics, especially β-lactams, and has been demonstrated to be effective in vitro against *P. aeruginosa* and enterobacteria [7]. Corvec et al. compared the activities of fosfomycin, tigecycline, colistin and gentamicin (alone and in combination), against a CTX-M15-producing strain of *Escherichia coli* in vitro and in a foreign-body infection model [10]. Fosfomycin was the only single agent, which was able to eradicate *E. coli* biofilms (cure rate, 17% of implanted, infected cages). In combination, colistin plus tigecycline (50%) and fosfomycin plus gentamicin (42%) cured significantly more infected cages than colistin plus gentamicin (33%) or fosfomycin plus tigecycline (25%) ($p < 0.05$). The combination of fosfomycin plus colistin showed the highest cure rate (67%), which was significantly better than that of fosfomycin alone ($p < 0.05$). Therefore, the authors conclude that the combination of fosfomycin plus colistin is a promising treatment option for implant-associated infections caused by fluoroquinolone-resistant GNB, but the effectiveness of this combination should be assessed in vivo.

Other potential therapeutic alternatives are combinations that include tigecycline or rifampin for their demonstrated in vitro synergism with several drugs. Tigecycline has been used for carbapenemase-producing gram-negative PJIs, although bone concentrations of the drug are usually lower than the minimum inhibitory concentrations of these bacteria [11]. Drapeau et al. recently described a literature review of 19 clinical studies on the use of rifampin in treatments for multidrug resistant gram-negative (MDRGN) bacterial infection [12]. Nonetheless, the real clinical benefit of using rifampin-containing therapies for MDRGN bacteria in terms of clinical outcome and survival rates remains to be defined.

The development of new agents (ceftazidime/avibactam, aztreonam/avibactam, cefiderocol, ceftolozane/tazobactam) with activity against MDRGN bacteria will provide important therapeutic options for clinicians, but definitive data showing clinical efficacy is currently lacking [13].

The efficacy of intrawound tobramycin powder in terms of eradicating a known bacterial contamination in an *Escherichia coli*-infected rabbit spinal implantation model was assessed, with the researchers concluding that intrawound tobramycin eliminated *Escherichia coli* surgical site contamination [14].

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Authors: Steven Schmitt, Christopher Kepler

QUESTION 10: Is there a difference in the efficacy of vancomycin beads versus vancomycin powder for spinal implant infections?

RECOMMENDATION: It is unclear whether there is a difference in the efficacy of vancomycin beads versus vancomycin powder for spinal implants infections.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 93%, Disagree: 0%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Currently, there are no studies comparing or individually evaluating the efficacy of vancomycin powder and vancomycin beads for the treatment of infections following spinal instrumentation.

3.3. TREATMENT: IMPLANTS

Authors: Pouya Alijanipour, Caroline Granger

QUESTION 1: Should a cage be removed in patients with postoperative spine infection?

RECOMMENDATION: No. The interbody cage can be maintained in the absence of clinical and radiographic signs of loosening or displacement of the cage or compression on neural and vascular structures. However, the cage should be removed if the infection persists despite salvage attempts consisting of irrigation and debridement procedures combined with intravenous antibiotic treatment.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 73%, Disagree: 0%, Abstain: 27% (Super Majority, Strong Consensus)

RATIONALE

The incidence of surgical site infection in the presence of an interbody cage depends on various factors including the type of approach (anterior, posterior or lateral) and whether the cage is stand-alone or associated with posterolateral instrumentation fusion. Series with stand-alone posterior lumbar interbody fusion (PLIF) or anterior lumbar interbody fusion (ALIF) have lower infection rates (up to 3%) compared to those with long constructs in degenerative adult scoliosis (up to 11%) [1]. On the other hand, adding interbody fusion to posterolateral spinal fusion can be a risk factor for infection and a series of posterolateral fusion with interbody fusion reported higher incidence of surgical site infection compared to those without interbody fusion, most probably due to prolonged surgical procedure, increased blood loss and tissue damage associated with interbody fusion (0.3% versus 1.4%) [2].

Spondylodiscitis at the site of an interbody fusion can present with or without signs of superficial wound infection. If superficial infection does not exist, deep infection can be underestimated or ignored initially due to late presentation. In one report, the average time to diagnosis for spondylitis in patients with PLIF was 164.5 days (range 10–410 days) and time to diagnosis longer than three months was the only predictive factor of failure of intravenous antibiotic treatment and need for implant removal [3]. Moreover, the intervertebral disc tissue is a naturally avascular tissue, limiting the efficiency of immune response as well as efficiency of antibiotics for eradication of infection. Delayed treatment of cage infection can be associated with the risk of extension of infection to the neural elements as well as to the vital retroperitoneal organs and major vessels with disastrous consequences [4].

Cage removal is associated with a risk of interbody space collapse, foraminal narrowing, loss of alignment, progression of deformity, loss of fixation, instability and pseudoarthrosis [5]. On the other hand, inappropriate cage retention can establish bacterial colonization and biofilm formation on the surface of the implants, and diminishes the efficacy of antibiotic treatment [6]. Time of presentation (early versus late postoperative infection), chronicity and severity of symptoms are other considerable factors [7,8].

According to the published case series, in most cases of interbody cage infection, the cage can successfully be retained with an initial salvage attempt consisting of irrigation and debridement procedures combined with antibiotic treatment [1,9–15]. Although, there is no agreed definition criteria for failure of salvage treatment, the following conditions have been considered as indication of cage removal: presence of discitis, osteomyelitis, signs of cage loosening, epidural abscess, extension of infection to soft tissues and presence of bone loss [1,4,8]. Most of these criteria are based on the findings of advanced imaging such as computed tomography and magnetic resonance imaging. One study presented 10 cases with uncontrolled infection of interbody cage, all of which were placed via posterior

approaches. In 9 out of 10 cases, solid bone fusion was achieved via an anterior procedure consisting of cage removal and the use of autogenous iliac bone graft to fill the interbody space [16]. An anterior approach for removal of a posteriorly-placed interbody cage prevents complications associated with epidural scar tissue and fibrosis due to the inflammatory response to the original surgery and infection process [16].

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Authors: Christopher Kepler, Barrett Boody

QUESTION 2: Is there a length of time of infection beyond which instrumentation should be removed?

RECOMMENDATION: The data suggests that early infection can commonly be treated with implant retention and debridement followed by intravenous (IV) antibiotics and common oral antibiotic treatment. If the patient has achieved spinal fusion, the implants can be safely removed. In the setting of pseudarthrosis, thought should be given to removal of implants to eradicate infection followed by re-instrumentation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The primary goals of treating postoperative spinal surgical site infections (SSIs) are to eradicate the infection, maintain stability and achieve fusion (when warranted). While the decision to retain existing instrumentation in the setting of an acute infection may be necessary for maintaining stability or promoting fusion, this may jeopardize the surgeon's ability to completely eradicate the SSI. The preponderance of available evidence suggests the ability to both retain hardware and successfully eradicate the infection depends on the acuity of the presentation, with early diagnoses of SSI (within 30 to 90 days after index procedure) having higher rates of successful retention after debridement and IV antibiotics, while deep infections over one year commonly require removal.

Several studies have demonstrated successful eradication of infection with debridement and hardware retention for early-onset SSI. Patel et al. reviewed surgical debridement and retention of instrumentation in 17 patients with SSI after spinal arthrodesis ranging from 1 to 6 weeks after the index procedure, noting eradication of infection in all patients and successful fusion in 15 of 17 (88.2%) [1]. Sierra-Hoffman et al. reported successful instrumentation retention with early onset (< 30 days) SSIs with debridement and long-term antibiotics alone, noting eradication of infection in 17 out of 19 (89.5%) patients. However, six of the seven late infections (> 30 days) ultimately required instrumentation removal for eradication of the infection [2].

Pull ter Gunne et al. noted that their management of SSI involved aggressive debridement (89.3%) with hardware retention (if stable) and revision of hardware (if unstable), followed by an average of 40 days of antibiotics. With this protocol, 76% of their deep infections were eradicated with a single debridement, although no comment was made about the chronicity of the SSI prior to reoperation [3]. Kowalski et al. reported on 30 acute SSIs (< 30 days) with 80% successfully retaining implants with surgical debridement and IV antibiotics followed by oral suppressive antibiotics [4]. Tominaga et al. reviewed risk factors for unavoidable

removal of instrumentation after SSI < 90 days, finding that 12 of 16 cases successfully retained implants after debridement and IV antibiotics, but noted that 3 of 4 failures grew methicillin-resistant *Staphylococcus aureus* (MRSA) on operative cultures, compared with only 1 of 12 successfully-treated cases diagnosed with MRSA [5]. Nunez-Pereira et al. reported 43 patients with acute SSI after posterior spinal fusion requiring debridement and IV antibiotics for at least 8 weeks, finding 90.7% survival (survival to follow-up timepoint with avoidance of implant removal) at 6 months, 85.4% at 12 months, and 73.2% out to 4 years [6]. Multivariate analysis revealed a significant risk of treatment failure in patients who developed sepsis (hazard ratio 12.5 [95% confidence interval 2.6 to 59.9]; $p < 0.001$) or who had more than three fused segments (hazard ratio 4.5 [95% confidence interval 1.25 to 24.05]; $p = 0.03$) [1].

Accurately predicting the number of required debridements to eradicate the SSI can be challenging. Thalgott et al. identified that initial debridement culture results and the patient's comorbidities, including systemic disease, immunocompromise and malnourishment, are prognostic for the number of debridements required. Healthy patients with less virulent bacteria commonly required a single debridement, while immunocompromised hosts, multiple and/or more virulent organisms, and polymicrobial infections often require multiple debridements [7]. DiPaola et al. evaluated risk factors predicting multiple debridements, identifying MRSA and distant site infection as the strongest predictors, and diabetes mellitis, the presence of instrumentation, use of allograft and posterior lumbar spine location also displaying significant associations [8].

Conversely, delayed diagnoses of SSI commonly require implant removal for successful infection eradication. Hedequist et al. found all 26 cases with SSIs presenting greater than 3 months postoperatively required implant removal to definitively clear the infection [9]. Similarly, Kowalski et al. reported 7 out of 13 late diagnoses of SSI (> 30 days) failed debridement and initial implant retention, requiring secondary surgery for implant removal [4]. Tsubouchi et al. noted that although 29 out of 43 patients successfully retained spinal implants for SSI < 30 days postoperatively, only 4 of 12 patients diagnosed later than 30 days and 0 of 4 patients diagnosed later than 90 days successfully retained implants [10]. Garg et al. reported on 42 patients with deep infection more than 1 year postoperatively after spinal fusion, noting that 41 required implant removal and retention attempted in 1 patient failed. Additionally, 27 of the 42 patients showed *C. acnes* on intraoperative cultures [11].

Ho et al. reviewed their experience with pediatric SSI after instrumented fusion for scoliosis, noting that 43 out of 53 (81%) patients had retained implants at their first irrigation and debridement. They found a significant increase in secondary debridement required with implant retention (47%) in comparison to implant removal at the first irrigation and debridement (20%). However, implant removal was associated with a 10-degree or greater curve progression in 60% of patients [12]. Balancing the need for spinal stability and prevention of deformity progression or pseudarthrosis against a more complete eradication of infection remains a case-by-case decision guided by surgeon experience.

Mok et al. reviewed the functional impact of infection after posterior spinal fusion with 12 early (< 90 days) and 4 late (> 90 days) SSIs undergoing debridement with retention of instrumentation, and reported no significant difference in long-term SF-36 outcomes compared with non-infected controls at an average follow-up of 56.7 months [13]. Kuhns et al. similarly compared quality of life (QOL) scores between infected posterior cervical fusions requiring reoperation to noninfected matched controls. While the total projected costs were increased ($21,778 vs. $9,159) and 6-month QOLs were significantly lower for the infected cohort, no significant differences were found in QOL outcomes at the 12-month follow-up [14].

Recent literature has questioned the significance of time-based decision-making for implant removal following SSI and instead has turned to advanced imaging to understand the causes of implant retention failures. Kanavama et al. evaluated preoperative magnetic resonance imaging (MRIs) in SSIs, noting that once vertebral osteomyelitis and/or intervertebral abscess were evident in MR images, all the hardware should be removed [15]. Six of seven patients without osteomyelitis or intervertebral abscess successfully retained implants, while 9 of 13 patients with osteomyelitis or intervertebral abscess ultimately required implant removal and three of four patients who retained implants resulted in loss of fixation stability [15].

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Author: Wesley Bronson

QUESTION 3: Should bone graft be removed in patients with postoperative spine infection? If yes, should a distinction be made between allograft and autograft?

RECOMMENDATION: Bone graft need not be routinely removed following irrigation and debridement, especially if partially incorporated. However, loose or purulent graft should be considered for removal. Retained allograft may increase the risk for requiring repeat debridement compared to autograft.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 87%, Disagree: 0%, Abstain: 13% (Super Majority, Strong Consensus)

RATIONALE

No literature could be found that directly stratified patients who had bone graft retained versus removed. Weinstein et al. studied 46 postoperative infections in 2,391 patents [1]. In their regimen, bone graft material that appeared viable was left in place and instrumentation was retained as well. After six weeks of antibiotics, all of the wounds healed. Massie et al. similarly reported that bone graft may be retained and rarely is it necessary to remove all bone graft [2]. Ahmed et al. also showed in their retrospective review that debridement and antibiotics with implant and bone graft retention (allograft and autograft) can result in complete eradication of infection [3].

Nonetheless, bone graft loosened by irrigation may be removed. It seems rational that unincorporated bone graft and loose, dead bone serves as a continued nidus for infection and as such should be removed [4]. Multiple authors thus recommend thorough irrigation and debridement with removal of nonviable, purulent and loose graft material. However, this appears largely based upon intuition and not strict evidence.

There is limited evidence that perhaps autograft is better tolerated in the setting of an infection. Dipola et al. created a predictive model to differentiate patients requiring one versus multiple debridements [5]. The use of bone graft rather than autograft was shown to be predictive of requiring multiple debridements. Perhaps, therefore, closer attention ought to be given to the viability and infection burden in patients with allograft. However, no specific recommendations can be given and this should be considered on a case-by-case basis, with considerations of host status, infectious organism and infection burden.

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Author: Yvonne Achermann

QUESTION 4: What are the indications for implant retention or removal of hardware in spinal infections?

RECOMMENDATION: In early or acute infections, debridement with retention of the implant might be possible and should always be favored, as removal of the implant carries a great risk for non-fusion despite the risk of chronic low-grade infections with possible implant loosening. In late infections, removal is recommended if feasible.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 87%, Disagree: 7%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Similar to periprosthetic joint infections (PJI), several authors recommend that in early spinal implant-associated infections (within one month after surgical treatment or symptom duration less than three weeks), a debridement with retention of the implant constitutes a sufficient treatment strategy [1–5]. However, their recommendation is based on a retrospective, small case series of patients. There are also reports describing continuous irrigation in early infections [6,7], but no controlled studies with non-continuous irrigation are published.

In chronic infections, which are often caused by low-grade pathogens, such as coagulase-negative staphylococci or *Cutibacterium acnes*, removal of implants is regarded as the treatment of

choice [3,8–10]. Infections with low-grade pathogens often present in a delayed fashion so that the implant-associated biofilm is mature and bacteria in the biofilm cannot be killed by antibiotics only or debridement with retention of the implant. In addition, patients with chronic infections often present with pseudarthrosis [11]. Hedequist et al. retrospectively reported on 26 chronic infections in which curing was only achieved after removal of the implants with prior unsuccessful treatment attempts with implant retention [12]. In six patients, hardware reimplantation was needed due to progression of the underlying deformity (curve progression). Implant removal carries the risk of disc collapse, lack of fusion, loss of normal lordosis and pseudarthrosis [3,13], which have to be considered.

There are no recommendations as to whether only the dorsal instrumentation or the interdiscal cage should be removed as well for successful treatment. In addition, no prospective clinical trials comparing removal versus retention of the implant in chronic infections exist. Lall et al. nicely summarized treatment regimens of deep wound infections after spinal instrumentation [14].

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Authors: Barrett Woods, Maja Babic

QUESTION 5: Is there a role for one-stage exchange of hardware in the presence of spinal infections?

RECOMMENDATION: There is insufficient data on one-stage exchange of hardware in the presence of spine infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Evidence supports debridement and implant retention in early implant-associated infections. In delayed implant-associated spine infections, evidence favors hardware removal followed by a course of antibiotics. Even if solid fusion is present, significant loss of correction can occur, posing the question of whether one-stage exchange of hardware would be adequate [1]. It is established that placing spinal instrumentation into an infected spine is safe when necessary for spinal stability and eradication infection, with low recurrence and reoperation rates [2]. Data on hardware one-stage exchange in deep infections with instrumentation is lacking.

Infection following instrumented spinal fusion can result in significant morbidity to the patient, resulting in prolonged hospitalization, chronic pain and need for revision surgery. In addition to the morbidity, the economic impact of this type of infection to the healthcare system and patient cannot be overstated. Several risk factors associated with the development of surgical site infection (SSI) following instrumented spinal fusion have been identified [2–4]. Management of superficial infection typically consists of oral or intravenous (IV) antibiotics, with surgical intervention reserved for failure of medical management, symptomatic deep infections or draining wounds with soft tissue compromise. Treatment of deep infections surgically is complicated by the presence of spinal instrumentation. Eradication of infection is the primary goal of surgery, however premature removal of instrumentation can result in pain, pseudoarthrosis and deformity [5–7].

Several series have been published illustrating successful treatment of deep wound infection with irrigation debridement and retention of original instrumentation [8–14]. Picada et al. published on a series of 26 patients with infection following instrumented spinal procedures, with 24 (92.3%) successfully treated with surgical debridement, intravenous antibiotics, nutrition optimization and primary or delayed secondary closure [13].

Kowalski et al. retrospectively reviewed the management of 81 patients with infections following spinal instrumentation. The

cohorts were defined by early and late onset infection [9]. Of the patients with early onset infection, 28 of 30 were treated with irrigated debridement and retention of hardware with predicted probability of treatment success at two years being 71%, while patients with late onset infections required removal of hardware to achieve an 84% probability of treatment success at two years. Maruo et al. retrospectively reviewed a series of 225 consecutive patients with SSIs following spinal surgery [10]. Of those, 126 or 76% were successfully treated with surgical debridement, IV antibiotic therapy and retention of hardware. Failure of this treatment strategy was associated with late infection, long constructs with pelvic fixation, *Propionibacterium acnes* speciation and poly-microbial infection.

Nunez-Pereira et al. published on a series of 43 consecutive patients with SSI treated with surgical debridement and targeted antibiotic therapy with retention of original instrumentation [11]. At a 26-month follow-up, 10 patients (23.3%) failed, requiring removal of hardware, or died. Multivariate analysis found treatment failure associated with sepsis and long constructs (> three levels fused). Tominaga et al. published a retrospective series of 16 consecutive patients who developed SSI following spine instrumentation over an eight-year span [15]. Twelve of the 16 cases (75%) were successfully treated with retention of hardware, with failure associated with long instrumented constructs, previous spinal surgery, low preoperative hemoglobin, high preoperative creatinine and methicillin-resistant *Staphylococcus aureus* (MRSA) speciation. DiPaola et al. developed a predictive model determining the need for single versus multiple irrigation and debridement procedures to successfully eradicate postsurgical spinal infection [8]. The authors identified MRSA-positive cultures, bacteremia, non-autogenous bone graft and diabetics as predictive for requiring multiple debridement procedures. Vacuum-assisted closure (VAC) can be used to help facilitate wound healing following irrigation and debridement with hardware retention for spinal infection [16].

There are several studies illustrating the successful management of SSI following spinal instrumentation with surgical debridement, IV antibiotic therapy and primary or delayed secondary closure. Factors consistently associated with treatment failure included late infection, long constructs with pelvic fixation, *C. acnes*/MRSA speciation and bacteremia. Patients with these characteristics should likely have removal of hardware in addition to surgical debridement. Multiple debridement procedures may be required to successfully treat the infection, which can be assisted by the use of a wound VAC.

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3.4. TREATMENT: WOUND CARE

Authors: Carles Pigrau, Gregory Schroeder

QUESTION 1: Should infected wounds undergo primary closure or a two-stage closure?

RECOMMENDATION: The current recommended practice for spine wounds remains primary closure in the majority of postoperative infections. However, there may be circumstances when primary closure of the wound may not be possible or preferred. This may include patients with grossly contaminated traumatic wounds, patients with persistent wound drainage when attempts to address drainage have failed or patients with severe soft tissue loss when primary closure is not possible.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 93%, Disagree: 0%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Following surgery, wounds are typically closed in a primary fashion. Alternative methods of wound closure include secondary closure and delayed primary closure. Secondary closure is when wounds are left to close naturally on their own. Delayed primary closure (DPC), a combination of secondary and primary closure, is when a wound is cleaned and left open until infection is controlled, followed by surgical closure of the wound. Delayed primary closure is only used on occasion, typically involving contaminated traumatic injuries.

In their prospective randomized study, Singh et al. found that patients undergoing delayed primary closure of contaminated abdominal wounds related to hollow viscus perforation had lower infection rates (17.5%) and shorter hospital stays (18.1 days) when compared to patients undergoing primary closure (42.5% infection and 20.7 days) [1]. Chiang et al. found a similar result for treatment of perforated appendicitis. Patients randomized to primary closure had an infection rate of 38.9% and an 8.4-day length of stay, while patients randomized to delayed primary closure had an infection rate of 2.9% and a 6.3-day length of stay [2].

DPC has also been shown to result in no long-term issues and not be associated with a higher incidence of complications in pediatric liver transplant recipients [3]. Orthopaedic surgeons are familiar with DPC in the context of fasciotomy wounds in patients with compartment syndrome when delayed primary closure is utilized [4,5].

There are, however, no high-level studies related to the role of DPC in spine surgery. In the absence of concrete evidence, and in borrowing from general surgery and other fields of orthopaedics, we feel that primary closure of a wound is the most preferred method of dealing with wound issues in spine patients. However, there may be circumstances when primary closure of the wound may not be possible or preferred. This may include patients with grossly contaminated traumatic wounds, patients with persistent wound drainage when attempts to address drainage have failed and in patients with severe soft tissue loss when primary closure is not possible.

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Author: Wesley Bronson

QUESTION 2: What is the indication for muscle advancement flaps in patients with spinal infections?

RECOMMENDATION: Muscle advancement flaps are useful to help close wounds with exposed hardware as well as those which fail local treatment/vacuum-assisted closure (VAC) therapy and to help improve infection eradication.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 93%, Disagree: 0%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Multiple risk factors exist for wound complications following spinal surgery, including diabetes, chronic obstructive pulmonary disease, resection of neoplasm with excision of significant soft tissue and prior radiation. Additionally, infection is often complicated by loss of soft tissue and poor tissue viability, which leads to an inability to close the wound overall, resulting in exposed hardware [1,2].

Even if the wound is able to be closed primarily or following VAC therapy, it is important to recognize that the same factors that led to the infection and wound breakdown in the first place still exist [3]. To that end, local or vascularized muscle flaps provide multiple advantages over simple wound closure or delayed primary closure. Muscle flaps have been shown to increase blood flow and oxygen delivery, and decrease bacterial load [4–6].

It seems rational that wounds that are completely unable to be closed due to large soft tissue defects with exposed hardware or wounds that fail to close following VAC therapy are reasonable indications for flap coverage. But, the absolute indication for flap coverage following wound debridement in an otherwise closeable wound remains unclear. Multiple authors argue that it remains a reasonable option versus irrigation and debridement with immediate or delayed primary closure.

Dumanian et al. reviewed their experience with flap coverage for spinal wounds [7]. Fifteen patients in their group had postoperative wound dehiscence or infection, with 12 patients having exposed hardware. They were treated with either immediate local flap coverage or two to three days of dressing changes followed by flap coverage. Of the surviving 14 patients, 13 had healed wounds at final follow-up, and none required hardware removal. One patient on chronic steroids/immunosuppression had persistent infection treated with chronic suppressive antibiotics.

Chieng et al. performed a systematic review on the use of flaps for management of wound complications [8]. While several case reports and retrospective series present supportive data, the authors note that relying on the data is difficult as no level 1 or level

2 evidence exists. Additionally, there is a lack of comparative studies directly looking at flap coverage versus traditional wound closure techniques.

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Authors: Koji Yamada, Kazuhiro Kohata

QUESTION 3: What is the optimal irrigation solution (volume, type and frequency) during clean or infected spinal surgery cases?

RECOMMENDATION:

1. There is insufficient evidence to recommend for or against normal saline irrigation before closure for the purpose of preventing surgical site infection (SSI) in clean spinal surgery.
2. There is insufficient evidence to support recommendations for optimal volume, type and frequency of irrigation to prevent SSI in clean spinal surgery.
3. Consider the use of irrigation with an aqueous povidone-iodine solution before closure for the purpose of preventing SSI in clean spinal surgery.
4. There is insufficient evidence to recommend for or against chlorhexidine and antibiotic solution irrigation of incisional wounds for the purpose of preventing SSI in clean spinal surgery.
5. There is insufficient evidence to recommend a specific solution (volume, type and frequency) for irrigation in infected spinal surgery.

LEVEL OF EVIDENCE:

1. Consensus
2. Limited
3. Moderate
4. Consensus
5. Consensus

DELEGATE VOTE: Agree: 73%, Disagree: 7%, Abstain: 20% (Super Majority, Strong Consensus)

RATIONALE

1: Irrigation versus no irrigation

No randomized controlled trials (RCTs) or observational studies have compared incisional wound irrigation with normal saline versus no irrigation in clean spinal surgery.

One retrospective observational study evaluating 1,831 posterior lumbar interbody fusion (PLIF) procedures demonstrated a significantly higher risk of SSI with no local bone irrigation compared to those with local bone irrigation in multivariate analysis (odds ratio (OR): 5.248, p = 0.001) [1]. Two retrospective observational studies demonstrated no significant association between interbody irrigation with SSI compared with no interbody irrigation in those undergoing PLIF and lumbar microdiscectomy [1,2].

2: Optimal volume, type and frequency of irrigation for clean spinal surgery

No RCT has compared the amount of normal saline for irrigation to prevent SSI in spinal surgery. One observational study including 223 consecutive spinal operations in a single university hospital demonstrated a significant association with prevention of SSI (OR 0.08, 95%, confidence interval (CI) 0.01 to 0.61) with sufficient amount of saline (mean > 2,000 ml per hour compared with < 1,000 ml per hour) in a multivariate analysis [3].

No RCT or observational study has compared the frequency of irrigation to prevent SSI in spinal surgery.

A very low quality of evidence from two observational studies demonstrated a benefit of pulse pressure irrigation compared to bulb syringe irrigation with normal saline [4,5]. One study showed an advantage of decreasing wound contamination rate in PLIF surgical procedures (OR:6.35, p = 0.046) [4]. Another study showed significant decrease of postoperative infection by ten-fold (11% [28/261] vs. 0.7% [2/263], p < 0.001) by using pulsatile irrigation with vancomycin and ceftazidime prophylaxis for posterior spinal fusion surgeries in adolescent idiopathic scoliosis patients [5].

3 and 4: Optimal solution for clean spinal surgery

There is moderate-quality evidence from two RCTs and two observational studies that povidone iodine irrigation has a signifi-

cant benefit in reducing SSI risk in patients with primarily closed surgical incisions when compared to conventional normal saline wound irrigation [6–9]. In one RCT focusing on primary instrumented lumbosacral posterolateral fusion performed by the same surgeon, SSI was significantly lower in those who underwent 0.35% povidone-iodine irrigation compared with normal saline irrigation (0% [0/120] vs. 4.8% [6/124], p = 0.029), with no significant difference in fusion rate, wound healing, improvement of pain score, function score and ambulatory capacity [6].

In another RCT focusing on spinal surgery, SSI was significantly lower in those who underwent 0.35% povidone-iodine irrigation compared with normal saline irrigation (0% [0/208] vs. 3.4% [7/206], p = 0.0072) [7]. In one observational study comparing before and after the application of combination of 0.3% betadine irrigation with intra-wound vancomycin (VCM) powder (1 gm), the incidence of SSI significantly decreased after intervention (1.3% [15/1173] vs. 2.4% [30/1,252], p = 0.042) with a protective effect in multivariate analysis (OR 0.23, 95% CI: 0.06-0.86; p = 0.0287) [8]. In another observational study involving 950 spinal surgeries comparing before and after application of povidone-iodine and hydrogen peroxide solution irrigation, those irrigated with povidone-iodine and hydrogen peroxide solution were less likely to develop SSI compared with pre-intervention period (0% [0/490] vs. 1.5% [7/460]) [9].

No RCT or observational study has compared chlorhexidine or antibiotic solution irrigation to normal saline irrigation to prevent SSI in spinal surgery.

5: Optimal irrigation for infected spinal surgery

No RCT or observational study has compared incisional wound irrigation with no irrigation in infected spinal surgery.

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Author: Carles Pigrau

QUESTION 4: Is negative pressure wound therapy (NPWT) effective in the treatment of wounds that are left to heal by secondary intention?

RECOMMENDATION: There is no evidence that NPWT is superior to conventional standard dressing changes in the treatment of wounds that are left to heal by secondary intention.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 60%, Disagree: 20%, Abstain: 20% (Super Majority, Weak Consensus)

RATIONALE

Animal studies have shown that sub-atmospheric pressure improves the local wound environment through both direct and indirect effects. Sub-atmospheric pressure accelerates healing and reduces the time to wound closure and the incidence of wound infections [1,2]. NPWT removes interstitial fluid and improves lymphatic drainage and microvascular blood flow. It increases oxygen and nutrient delivery in the wound, facilitates removal of metabolic byproducts, increases granulation tissue formation and ultimately accelerates wound healing. Moreover, by isolating the wound from the surrounding environment, NPWT may reduce the colonization of the wound by bacteria and avoid superinfections, particularly in areas with high skin contamination rates such as the perineal and lower back spine area.

Predominantly observational studies, but also small trials (low quality of evidence), have suggested that rates of surgical site infection (SSI) may be lower if NPWT is used instead of conventional wound dressings [3]. In a meta-analysis of six randomized control trials including a systematic review, it was observed that the risk of SSI was reduced when NPWT was used (odds ratio 0.56, 95% CI 0.32 to 0.96) in both clean and clean-contaminated procedures. However, results were no longer significant for orthopaedic/trauma surgery [3]. In a Cochrane meta-analysis that compared NPWT with other types of wound dressing for persistently-draining wounds in skin graft patients, in orthopaedic patients undergoing arthroplasty and general/trauma surgery patients it was concluded that there is no evidence for the effectiveness of NPWT on the complete healing of wounds expected to heal by primary intention [4]. An up-to date systematic review in trauma patients concluded that, based on available observational studies, NPWT [5] was safe and showed an efficacy comparable to standard dressings [6]. The primary clinical advantages of NPWT in the trauma population are its ease of application, decreased

number of dressing changes and reduction in the complexity of subsequent reconstructive procedures [7–11].

In a 2013 systematic review of NPWT for spinal wounds, no randomized clinical trials were found that addressed the use of NPWT to treat wound healing or spine SSIs, nor as prophylactic wound treatment to prevent wound breakdown and infection [12]. The duration of NPWT therapy and the number of debridement and irrigation procedures performed before the definitive wound closure operation were variable. After this review, an additional non-comparative study [12] showed the benefits of this therapy among only 6 of 317 infections after surgery for spinal stenosis. An average of 5.1 debridement and irrigation procedures were performed before the definitive wound closure operation. Vacuum-assisted closure dressings were changed at 3-day intervals and the median duration was 15 days (range 9-24).

After the revision published in 2013, only one longitudinal cohort study addressed NWPT use as a prophylactic therapy for spinal wounds. It is a well-designed, retrospective longitudinal study, which includes 160 adult patients with thoraco-lumbar spine deformity undergoing multi-level thoraco-lumbar fusion [13]. A 50% decrease in the incidence of wound dehiscence was observed in the NPWT cohort (46 cases) compared to the non-NPWT cohort (114 patients) and the incidence of postoperative SSI was significantly lower (10.6% vs 14.9%, $p = 0.04$).

In conclusion, prophylactic use of NWPT may significantly reduce wound dehiscence and wound infection after long-segment thoraco-lumbar spine fusion. There is no further evidence addressing the superiority of NWPT therapy compared to standard dressings. NPWT is safe in cases without dural leaks, easy to apply, and it decreases the number of dressing changes and reduces the complexity of wound closure. All these factors favor its use in selected cases.

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PART IX

ELBOW

Section 1: Prevention

Section 2: Diagnosis

Section 3: Treatment

Prevention

Authors: Raul Barco Laakso, Samuel Antuña

QUESTION 1: What are the optimal prophylactic perioperative antibiotics for patients undergoing total elbow arthroplasty (TEA)?

RECOMMENDATION: Patients undergoing primary TEA should receive antibiotics that cover gram-positive and gram-negative organisms specific to the regionally encountered organisms. Peer-reviewed literature supports that cefazolin should be dosed based on body weight. Patients with methicillin-resistant *Staphylococcus aureus* (*S. aureus*) colonization should receive weight-based glycopeptide, preferably in combination with cefazolin. Patients with a true hypersensitivity reaction or adverse reaction that precludes the use of cefazolin should receive vancomycin or clindamycin.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive literature search of three online databases (PubMed/Medline, Google Scholar and Embase) was performed using the following MeSH search terms: "elbow," "elbow joint," "joint prosthesis," "arthroplasty" and "replacement."

Because of the evolution of TEA techniques, only articles from the last 10 years were selected, published from January 2008 until January 2018. On the basis of the titles and abstracts, two reviewers independently identified potentially relevant articles for review of the full text. The reference lists of the included articles were manually checked to avoid missing relevant articles. When the full text was obtained, the authors independently selected articles. Studies were not blinded for author, affiliation or source.

Inclusion and Exclusion Criteria

The included articles presented original data on patients who had undergone TEA. The diagnoses included the following indications: osteoarthritis, trauma/fracture, post-traumatic osteoarthritis, rheumatoid arthritis, hemophilia and other inflammatory diseases. Studies with a minimum duration of follow-up of two years and a minimum of 10 patients were included. Studies on revision operations were not included. Articles presenting the results of both revision and primary TEA were excluded unless the information for primary TEA could be extracted. Articles presenting the results for interposition arthroplasties, fully-hinged prostheses, hemiarthroplasty or partial resurfacing of the elbow were excluded. Review articles, expert opinions and surgical technique articles were excluded. When possible, studies comparing different groups were analyzed separately. The search was restricted to articles written in English. Some articles that represented institutional historical databases were included only once.

Data Extraction

After the initial assessment for inclusion, two reviewers extracted data from the included articles. The primary goal was to determine the rate of infection after TEA and the pathogen responsible to determine which is potentially the best antibiotic regimen.

The following parameters were recorded when available: numbers of patients and elbows, design of TEA implant, indication for TEA (e.g., primary osteoarthritis, rheumatoid arthritis, fracture, post-traumatic osteoarthritis or other abnormality), whether the prosthesis was linked or unlinked, the rate of infection and the pathogen responsible for the infection (known/unknown, single/multibacterial). When prophylactic antibiotics were reported, they were recorded. No other attempt was made to extract other data regarding other complications.

Data and Statistical Analysis

Different groups were established on the basis of the preoperative regimen and the causative pathogen, when known. The outcome measures were the rate of infection and the distribution according to the pathogen. When sensitivity antibiotic analysis was performed, this information was also analyzed.

Methodological Quality

The two authors assigned the methodological quality of the included studies according to the Center for Evidence-Based Medicine [1].

RESULTS

Articles

After the removal of duplicate articles, our initial search yielded 227 articles from Medline, Embase and Google Scholar. After title and abstract evaluation, a list of 56 articles was created for full review. After full review, 35 studies were deemed suitable for further evaluation and data collection.

Five studies recorded different articles from an institutional database and a national arthroplasty registry, all being level IV evidence. There were no prospective case series or randomized, controlled trials. Two studies were disregarded as they offered duplicate information [2,3]. Data was extracted into a standard worksheet for further analysis.

Infection Rates and Pathogen Assessment

A total of 303 infections were recorded out of 6,681 patients, for a mean infection rate of 5.6%. Of these, 301 were considered by the authors to be a deep infection for an infection rate of 5.2%, with the other two corresponding to superficial infection.

A pathogen was identified in only five studies. It was not specified if the infection was mono- or polybacterial in all reported case

series. Large et al. reported four cases of deep infection. Two were positive for *Staphylococcus aureus*, one for *Staphylococcus epidermidis* (*S. epidermidis*) and one with no growing organism but a clinical diagnosis of infection [4]. Antuña et al. reported on the outcome of semiconstrained TEA after fracture of the distal humeral and observed 3 infections in 16 patients, 2 being positive for *S. epidermidis* and 1 having negative cultures [5].

Peden et al. reported on the outcome for TEA for an ankylosed or fused elbow, reporting 3 infections out of 13 cases. One occurred perioperatively and the other occurred at 2 and 15 years. Two cases were diagnosed with *Staphylococcus coagulase negative methicillin-resistant* and *S. aureus* [6]. Tachihara et al. reported on the outcome for TEA for rheumatoid arthritis and reported on three infections positive for *enterobacter*, *pseudomona* and *S. aureus*. In all of those cases, the infection was considered monobacterial [7].

Curiously, in a clinical series reporting on 20 elbows diagnosed with periprosthetic joint infection, Streubel et al. reported that 6 out of 21 infections were polymicrobial [8]. In that series, the most frequent pathogen was S. Coagulase-negative (13 patients) followed by *S. aureus* (9 patients) and *Corynebacterium* (3 patients). These patients were initially treated with vancomycin in 10 cases, cefazolin in 8, rifampin in 3 and ceftriaxone in 1 case [8]. This information is in accordance with other studies, although there is a risk of a partial duplicate patient population. In a group of 51 patients, Zarkadas et al. found 17 cases of *S. aureus*, 11 of *S. epidermidis*, 1 of *Serratia*, 1 of *Costiridium*, 1 of *Mycobacteria*, 1 of *C. acnes*, 10 multiorganism infections and 8 cases in which no bacteria was actually grown [9].

Although they are obviously universally used, only 4 of the 35 studies specified the use of prophylactic antibiotics. Of these, only 2 mentioned in their methods the type and dose of antibiotic (a first-generation and a second-generation cephalosporin prior to skin incision in both) [10,11]. Kodde et al. reported the use of 1 gm of intravenous cefazolin 30 minutes prior to skin incision and extended the use for 48 postoperative hour [10]. Lami et al. reported the use of systematic prophylactic antibiotic at induction using a second-generation cephalosporin with no further description. No other information regarding the duration of perioperative antibiotic therapy has been found.

Discussion

The available information is poor regarding infection as a complication after elbow replacement. Specific information on the pathogen, the type and dose of prophylactic antibiotic or the surgical prepping solutions used in cases complicated with an infection after elbow replacement are almost universally lacking in the analyzed studies. The reasons for this are unclear, but might be related to wording restrictions and focus on other aspects of research. Moreover, a definition of infection was not reported and different authors could have used different definitions.

Even though only four studies specified the use of prophylactic antibiotics, we assume these are universally used. Based on the scarce information found and our own clinical experience, first-generation cephalosporin seems to be the most widely used antibiotic. Other options could be used, based on allergies, intolerance or concomitant diseases. However, no sound conclusion can be extracted from literature on this regard.

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QUESTION 2: What is the evidence and recommendation for the use of antibiotic-laden bone cement (ALBC) in primary total elbow arthroplasty (TEA) or in revision TEA?

RECOMMENDATION: There is inadequate evidence to support the use of ALBC during primary or revision TEA.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 96%, Disagree: 0%, Abstain: 4% (Unanimous, Strongest Consensus)

RATIONALE

The response to the question regarding the value of ALBC in a primary and revision setting of TEA requires an understanding of several issues:

1. The specific answer to these questions referable to the elbow cannot be directly answered from the available literature addressing the elbow. Very little information exists for the

elbow, regardless of the level of evidence [1].

2. The clinical features of elbow pathology by definition place all TEAs "at risk," including the underlying diagnosis (a systemic inflammatory disorder or failed intervention for a post-traumatic condition). Primary osteoarthritis is not an indication for TEA as it is effectively treated with debridement. TEA for primary arthrosis was only performed in 18 patients over a 20-year period at the Mayo Clinic, representing about a 2% incidence in our institution [2].
3. Even the less common inflammatory etiology is at particular risk due to the virtual universal management with the immunocompromising disease remitting agents.
4. The subcutaneous location of the joint with little or no muscle protection places it at risk for wound healing problems, which has been documented to increase the likelihood of infection [3,4].
5. The subcutaneous nature and the less robust osseous structure of the elbow increases the complication rate of revision for infection, especially compromising triceps function in more than 25% of patients. In other words, the management of infection by surgical means is poorly tolerated at the elbow (level 4 and 5 evidence) [4].
6. The above observations are supported by the documented infection rate of the primary TEA to be around 5% (3) compared to 1–2% associated with primary hip or knee replacement, but similar to the infection rate of the revision procedures on these joints [4,5].
7. Finally, all the higher-quality literature on the subject relates only to knee and hip replacement with the preponderance of data relating to the knee.

Methodology

The question was addressed in the context of the above and the current literature relating to hip and knee surgery, primarily over the last 10 years. A PubMed literature review was conducted exploring level 1 and 2 randomized control trials, meta-analyses and national registry data. As noted above, all such studies relate only to hip and knee replacement. This review prompted a need for more detail in some instances, followed by level 3 and 4 case series and reports being included.

RESULTS

Use of ALBC in the Primary Total Knee Arthroplasty

- Currently, no conclusive evidence exists regarding the efficacy of antibiotic-loaded cement at the knee in uncomplicated, non-risk patients [6–11].
- Currently, based on the highest-level studies, no recommendation can be made regarding the routine use of antibiotic-loaded cement in primary knee arthroplasty.
- The justification is further weakened by poor cost-effectiveness data for primary knee [12,13], yet primary hip replacement may be cost-effective [14].
- As noted above, this recommendation has no bearing on the question at hand, as by definition all primary TEAs occur in an at-risk population.
- Consensus does exist that ALBC should be used in patients with a high risk of infection (Obesity, body mass index > 35, diabetes mellitus, revision total joint arthroplasty, operative time > 150 minutes, rheumatoid arthritis, a prior history of periprosthetic joint infection, organ transplantation and hemophilia) [5,6,15].

Use of ALBC in Hip Replacement Surgery

- Evidence [16–18], and consensus [19,20] is strong indicating that ALBC does statistically lessen the likelihood of infection after a primary hip replacement, independent of the at-risk patient [21–23].
- Evidence also indicates that ALBC decreases the incidence of deep infections at the hip and at the knee [24] and in hemi-replacement of the hip after fracture [25].
- Therefore, should antibiotic-impregnated cement be used:
  - **A. For primary TEA? Yes, based on:**
    1. Strong evidence supporting its use in primary hip replacement
    2. Strong consensus for ALBC in the at-risk patient and the features of the elbow defining it as an at-risk joint

    Confidence: Extrapolated: moderate; subjective: strong. 100%.
  - **B. For revision TEA? Yes, based on:**
    1. Moderate evidence for effectiveness in revision knee and hip surgery [5,26]
    2. Infection rate of revision TEA exceeds hip and knee revision, as well as increased difficulty and complication rates when treating an infected TEA [27]

    Confidence: Strong. 100%.

Additional Questions to Consider

1. **Which antibiotics(s) should be used?**
   - For primary and revision, combination therapy is recommended (total of 2 gm/40 gm monomer).
   - An aminoglycide, either 1 gm/40 gm cement gentamycin or tobramycin (tobramycin is much more expensive) and 1 gm/40 gm vancomycin.
   - Target likely-offending organisms [6]. Over the last 15 years in 231 infected elbows treated at Mayo Clinic: Coag – Staph – 22%; Staph A. 14% (data generated for this review – JSS).
   - A single low-dose gentamycin cement (1 gm/40 gm cement) may actually select an increase in coag – infections [6].
2. **Which cement should be used?**
   Palacos has better elution properties, but this does not seem to matter clinically.
3. **Will bacterial resistance develop?**
   No evidence of this to date [28].
4. **Will the altered mechanical properties of the cement affect loosening rate**?
   No evidence of this to date.

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QUESTION 3: Does previous surgery (arthroscopic, fracture fixation, other non-arthroplasty) increase the risk of subsequent elbow periprosthetic joint infection (PJI) after total elbow arthroplasty (TEA)?

RECOMMENDATION: There is an apparent increase in the percentage of infections among patients with a previous operation in the affected elbow joint, though the association is not robust and needs to be further analyzed.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A comprehensive literature search of three online databases (PubMed/Medline, the Cochrane database for clinical trials, and Embase) was performed using the following MeSH search terms: "elbow," "elbow joint," "joint prosthesis," "arthroplasty," "replacement," "elbow replacement," "elbow arthroplasty" and "elbow prosthesis."

Because of the evolution of TEA techniques, only articles published from January 2000 until September 2018 were reviewed. By the titles and abstracts, two reviewers independently identified potentially relevant articles for review of the full text. The reference lists of the included articles were manually checked to avoid missing relevant articles. When the entire text was obtained, the authors independently selected articles. Studies were not blinded for author, affiliation or source.

Inclusion and Exclusion Criteria

The included articles presented original data on patients who had undergone TEA. The diagnoses included the following indications: osteoarthritis, trauma/fracture, post-traumatic osteoarthritis, rheumatoid arthritis, hemophilia and other inflammatory diseases. Studies with a minimum duration of follow-up of two years and a minimum of five patients were included. Studies on revision operations were not included. Articles presenting the results of both revision and primary TEA were excluded unless the information for primary TEA could be extracted. Articles presenting the results for interposition arthroplasties, fully-hinged prostheses, hemiarthroplasty or partial resurfacing of the elbow were reviewed if they included information regarding the outcome of further treatment

with TEA with extractable outcome data. Review articles, expert opinions and surgical technique articles were excluded. When possible, studies comparing different groups were analyzed separately. The search was restricted to articles written in English, Spanish and French. Some articles that represent institutional historical databases were included only once.

Data Extraction

After the initial assessment for inclusion, two reviewers extracted data from the included articles. The primary goal was to determine the rate of infection after TEA and the pathogen responsible for determining the best potential antibiotic regimen.

The following parameters were recorded when available: numbers of patients and elbows, sex, age, design of TEA implant, indication for TEA (e.g., primary osteoarthritis, rheumatoid arthritis, fracture, post-traumatic osteoarthritis or other abnormality), whether the prosthesis was linked or unlinked, the rate of infection and the pathogen responsible. When prophylactic antibiotics were reported, they were recorded. Specific information regarding previous operations prior to arthroplasty was searched, as it was the focus of this review.

No other attempt was made to extract other data regarding other complications. Data regarding the number and type of surgical procedures before index TEA was collected and outcomes of these TEAs were extracted when available. Revision for infection was defined as removal of all or part of the arthroplasty or loosening that required removal regardless of the indication, or if a new TEA was implanted or excised.

Data and Statistical Analysis

Different groups were established by the preoperative regimen and the causative pathogen, when known. The outcome measures were the rate of infection and the distribution according to the pathogen. When sensitivity antibiotic analysis was performed, this information was also analyzed.

Methodological Quality

The two authors assigned the methodological quality of included studies according to the Center for Evidence-Based Medicine [1].

RESULTS

Articles

After the removal of duplicate articles, our initial search yielded 227 articles from Medline, Embase and Google Scholar. After title and abstract evaluation, a list of 56 articles was created for full review. After a full review, 35 studies were deemed suitable for further assessment and data collection.

There were no prospective case series and no randomized controlled trials. All were level IV evidence. Data were extracted into a standard worksheet for further analysis.

Prior procedures

Reporting of previous surgery before TEA was only available in six studies. Two hundred and one patients out of 291 (69%) were reported to have had prior surgery before TEA. The average rate of infection in these six studies was 11%, which is almost double to the reported rate of 5.5% in our concurrent systematic review (Table 1).

Kodde et al. reported on a series of 17 patients treated for post-traumatic arthritis with a cemented semi-constrained prosthesis, with a mean follow-up of 32 months. Fourteen patients had a prior operation consisting mainly in open reduction and internal fixation (nine cases, 64%), two patients had radial head resection, two had radial head prostheses implantation and one case had a medial epicondyle resection [2]. There was one case of infection (1%), but information is lacking regarding to which group it pertained. Additionally, the follow-up was short so that longer follow-up could increase the described rate of infection.

Baksi et al. reported on the use of a sloppy-hinge TEA for the treatment of fresh elbow fractures and non-unions. Eleven of the 41 cases reported had a previous failed internal fixation [3]. One of these patients suffered an infection that was treated with resection arthroplasty (1%) compared to one infection in 30 cases that did not undergo prior procedures (0.03%).

Throckmorton et al. reported on 84 patients with post-traumatic arthritis undergoing a semi-constrained TEA with a mean follow-up of nine years. The majority of this group of patients (90%) had prior surgery and the authors report seven deep infections without further information regarding the risk of preoperative surgery. The mean number of preoperative surgeries was three, so this group of patients may not be comparable to other studies [4].

Cil et al. reported the outcomes of a semi-constrained TEA for post-traumatic arthritis in 92 patients, of which 76 had previous surgery [5]. Of note, eight patients had a history of prior infection. At latest follow-up, five patients had an infection, all of which had had a previous operation. Interestingly, three of these patients had had a previous infection, so it is difficult to interpret if these were indeed a new episode or a reactivation of a latent infection.

Peden et al. reported on the outcome for TEA for an ankylosed or fused elbow, reporting 3 infections out of 13 cases [6]. One occurred perioperatively and the other happened at 2 and 15 years. Two of the three cases had previous surgery, but the type of surgery is not explicitly stated.

Sorbie et al. reported on a series of 44 unlinked TEA for hemophilic arthritis, rheumatoid arthritis or posttraumatic arthritis [7]. Sixteen patients had had a previous operation in the elbow and one of the seven infections occurred in a patient with post-traumatic arthritis and history of a previous operation. Once more, no reference to the number or type of previous operations was provided.

In a landmark paper, Morrey et al. reported on the outcome of 14 patients with an infection after TEA out of a group of 156 patients (9%) [8]. The rate of infection was 8 out of 99 patients without previous surgery compared to 6 out of 49 patients that had prior surgery (8% vs. 12.2%). This relationship was not statistically significant, alone. If only patients with previous surgery and rheumatoid arthritis were analyzed, the authors found a significant association, but the number of patients is so small that these findings should be interpreted with caution. Additionally, two of the patients with rheumatoid arthritis and prior surgery were on steroids.

The authors defined infection as deep sepsis that included different clinical and laboratory findings.

Conclusions

There is insufficient information regarding the influence of previous surgery on the incidence of infection after total elbow arthroplasty. Inadequate reporting regarding the number of procedures, the type of procedures and other patient-associated factors makes achieving definitive conclusions difficult. In a landmark paper, Morrey et al. highlighted the association of prior operation with the development of a periprosthetic joint infection after TEA. However, even though there is an apparent increase in the percentage of infections among patients with a previous operation, the association is not robust and needs to be further analyzed.

TABLE 1. Summary of information regarding the rate of infection after TEA when having prior surgery

Author, Year	Indication	Arthroplasty	Number of Cases	Number of Infections	% Infection	Number of Previous Surgeries	Additional Information
Kodde et al., 2013	PT	Coonrad-Morrey	17	1	5.8	14	None
Baksi et al., 2011	PT	Baksi sloppy hinge	41	2	4.9	11	1 infection in 11 PTs w/ prior surgery vs. 1/30 w/o prior surgery
Throckmorton et al., 2010	PT	Coonrad-Morrey	84	7	8.3	76	None
Sorbie et al., 2011	RhA/ PT/ Hemophilia	Sorbie	44	7	17%	16	1 infection with prior surgery (PT)/ 6 had infection immuno-suppression (RhA)
Peden et al., 2009	10 PT/ 3 RhA	Coonrad-Morrey	13	3	23%	8	2 of 3 infected had prior surgery
Cil et al., 2008	PT	Coonrad-Morrey	92	5	5.4	76	All 5 infections had prior surgery (3 had infection prior to index TEA)

PT, post-traumatic; RhA, rheumatoid arthritis; TEA, total elbow arthroplasty

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Diagnosis

Authors: Ilya Voloshin, Theodore Blaine

QUESTION 1: Is there a role for preoperative joint aspiration in the evaluation of the painful elbow arthroplasty for periprosthetic joint infection (PJI)?

RECOMMENDATION: Preoperative joint aspiration can play a role in the evaluation of the painful total elbow arthroplasty (TEA) suspected for infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

In a patient with painful TEA and the presence of prosthetic loosening on the radiographs, PJI is high on the list of differential diagnosis. PJI remains one of the major failure modes for TEA. Joint aspiration has not been evaluated at length as a diagnostic test in TEA, with only a few studies examining its role and usefulness in the identification of infection of the joint [1–3]. Although joint aspiration has not been specifically evaluated as a diagnostic test in TEA, the value of this diagnostic approach has been proven in the workup of patients with hip and knee arthroplasty [4].

Gille et al. reported that in five of six infected elbows, positive joint aspiration cultures were found, and cultures of the sixth elbow, which had previously been treated with antibiotics, tested positive for infection at the time of revision [2]. There is little data on the role of joint aspiration in evaluating infection in TEA, however, it has been shown to be useful in identifying patients with PJI in hip and knee arthroplasty patients [4].

When aspirated, the obtained synovial fluid should be sent for white blood cell (WBC) count, with particular attention to the differential (% polymorphonuclear neutrophils). In addition, the fluid should be sent for aerobic and anaerobic cultures. Elevated synovial fluid WBC count is highly suggestive of PJI [5]. The hip and knee arthroplasty literature demonstrated excellent sensitivity and specificity of synovial WBC for the diagnosis of chronic PJI [6–11]. Based on that literature, the proceedings of the International Consensus on PJI recommends the following thresholds for synovial fluid tests for chronic PJI: WBC > 3,000 cell/microL and % PMN of 80% [12]. For acute PJI, the recommended thresholds are the following: WBC > 10,000 cell/microL and % PMN of 90% [12].

Gram stains lack sensitivity and specificity, and are not routinely recommended [13]. Cultures remain the most effective method for specific organism identification. However, despite a high specificity, culture has poor sensitivity and a negative culture does not rule out the diagnosis of PJI [14–18]. For isolation of the infecting organism, aerobic and anaerobic cultures of the obtained samples should be performed [19,20]. The addition of Acid-Fast Bacilli (AFB) and fungal cultures can also be considered in patients with atypical infection and a possibility for these infections. Additionally, incubating cultures for a longer period (21 days) may assist in identifying fastidious, slow-growing organisms such as *Cutibacterium acnes* [21].

Despite the lack of adequate studies in the TEA literature, and borrowing from the hip and knee arthroplasty, we recommend that aspiration of elbow joint suspected of infection should be part of the diagnostic work up. The synovial fluid obtained should be sent for routine culture (which may need to be kept for 14-21 days), WBC count, determination of neutrophil percentage and possibly molecular analyses for identification of the infective organisms.

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Authors: Mark Mighell, Mark Frankle

QUESTION 2: What is the role for serum erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) or white blood cell (WBC) count in the evaluation of an elbow arthroplasty for periprosthetic joint infection (PJI)?

RECOMMENDATION: ESR, CRP and WBC play a role in screening and monitoring for PJI, though evidence is limited regarding specific thresholds and strategies to guide the surgeon when interpreting these values.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 95%, Disagree: 0%, Abstain: 5% (Unanimous, Strongest Consensus)

RATIONALE

When in the evaluation stage of a suspected PJI, these laboratory markers are often combined with the clinical findings and joint aspiration to increase confidence of PJI [1–9]. In isolation, ESR and CRP may be difficult to interpret, especially in the setting of a medically complex patient with underlying conditions such as rheumatoid arthritis or with atypical infectious organisms such as fungi [2,3]. In monitoring for resolution of an infection after initial explantation, these laboratory markers are utilized again in concert with clinical factors, and it is important to trend these over time [5]. If the values have not normalized at the time of subsequent surgery with plans to reimplant, a repeat debridement and washout is advised along with the trending of values over time.

Despite the lack of multiple randomized clinical trials reflecting the utility of ESR, CRP and WBC measurement and monitoring in the patient with PJI of the elbow, several retrospective studies demonstrate the usefulness of integrating these values into the treatment plan. Also, the importance of these markers has been incorporated into the recommendations of the American Academy of Orthopaedic Surgeons for the treatment of PJI in the hip and knee [7,10]. This recommendation is rated as "limited" due to the lack of large, high-quality studies addressing PJI in the elbow specifically, rather than adapting already-published data from other joints, though these results are useful as they may be extrapolated to the management of elbow PJI.

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QUESTION 3: What is the role of intraoperative histology examination in the evaluation of an elbow arthroplasty for periprosthetic joint infection (PJI)?

RECOMMENDATION: Intraoperative histology for the evaluation of elbow PJI in isolation is not sufficient for the diagnosis of infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 4%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

There are a number of studies related to the use of histologic examination for the diagnosis of PJI in hip and knee arthroplasty [1–4]. The available literature suggests that although histology cannot be used as a standalone test for the diagnosis of PJI, it does provide valuable information in the work-up of patients with suspected PJI (in fact, the MusculoSkeletal Infection Society (MSIS) workgroup included histological examination as a criterion for its diagnosis) [5,6]. The controversy that exists is what constitutes a positive histology [4]. Currently, based on the MSIS criteria, the presence of more than five neutrophils in more than five high-power fields is indicative of positive histology. The latter is based on examination of periarticular tissues for the diagnosis of infection and the role of histology during reimplantation to assess the presence of persistence infection is less well studied.

The role of histology in the workup of patients with painful total elbow arthroplasty (TEA) is less well known. Our extensive search of the literature revealed only one study that specifically examines the subject of histology in the diagnosis of infected TEA [7]. This study was a retrospective analysis of 208 patients undergoing revision TEA. The sensitivity of histology in the diagnosis of PJI was 51.3%, with a specificity of 93.1%. The positive predictive value of histological examination was 60.6% with a negative predictive value of 90.2%.

Among the cohort, 65 (31%) did not have either histology or cultures taken at the time of revision, which raises the question of selection bias. The sampling sites of the histologic specimens were not standardized and were performed at the discretion of surgeon, averaging less than two samples per patient. Finally, the gold standard to define infection was the presence of a single positive intraoperative culture. Within these limitations, the data suggests that when intraoperative histology demonstrates acute inflammation (according to the criteria of Mirra et al. [8]) the probability of infection is high, but the absence of the acute inflammation does not rule out infection.

Based on the literature (mostly from hip and knee arthroplasty) and our understanding of the challenges that exist in the work-up of patients with painful TEA, we recommend that histological examination of tissues from around the elbow be part of the workup of patients undergoing revision TEA.

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Authors: Michael McKee, Graham King

QUESTION 4: Is there a role for sonication of retrieved implants from an elbow in the diagnosis of a possible periprosthetic joint infection (PJI)?

RECOMMENDATION: At present, there is no evidence to support the routine use of sonication of removed elbow implants to improve the diagnostic accuracy or yield of cultures in the diagnosis of elbow PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Sonication involves the application of high-frequency ultrasound (approximately 40 kHz) to a retrieved implant in an ultrasound "bath" of appropriate fluid medium. The liquid medium from the bath is then collected and centrifuged, and these aliquots are

cultured with conventional techniques. The concept is that organisms ensconced in a biofilm on the implant are loosened or released by this process, and are more readily cultured.

There was some promising initial evidence from retrospective reviews that the sonication process increased the number of positive cultures, especially in patients who had been receiving antibiotics, or those who had previously negative cultures despite clinical and serological evidence of infection. However, these studies focused on lower extremity arthroplasty. A paper by Holinka et al. noted improved diagnostic accuracy with sonication ($p = 0.008$) compared to conventional cultures, but none of the 60 patients studied had an elbow prosthesis [1]. Similarly, a study by Achermann et al. reported on only one elbow implant in 37 cases, which significantly limits the applicability of this information to the upper extremity [2].

There is only one study in the literature that is specific to the elbow. A review of 27 presumptively uninfected and 9 infected patients with a prosthetic elbow noted that while sonification of removed elbow arthroplasty implants had a sensitivity of 89% and a specificity of 100%, this did not differ significantly from the results of standard microbiological culture techniques at their institution (sensitivity 55%, specificity 93%, $p = 0.18$ and $p = 0.16$, respectively). While this may represent a "beta-error" in which a true improvement in the yield of sonication is obscured by insufficient numbers to prove statistically significance, in the eight years since this paper was published, we were unable to find a more definitive or compelling study [3,4].

A larger study of 53 shoulder arthroplasty patients examining the results of sonication of retrieved upper extremity implants has recently been published by Grosso et al. [5]. They found that the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy of the cultures were not improved by sonication (US) when compared to standard (S) techniques: Sensitivity 96% (S) versus 96% (US), specificity 75% (S) versus 64% (US), PPV 77% (S) versus 71% (US), NPV 95% (S) versus 95% (US) and accuracy 85% (S) versus 79% (US). None of these differences were statistically significantly different. Additionally, it is well-recognized that the microbiological flora of the shoulder, and the subsequent infections that result from it, are distinctly different than that of the elbow. Therefore, it is not advisable to directly compare (or extrapolate the findings of) one joint to the other.

To conclude, at the present time there is insufficient evidence to either support or refute the utility of routine sonication of prosthetic elbow implants removed at the time of surgery in order to increase the yield or accuracy of cultures. Until a sufficiently-powered, prospective study has been performed demonstrating the efficacy of sonication to diagnose infection for revision elbow arthroplasty, we cannot support the routine use of this technology.

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Authors: Mark Morrey, Shawn O'Driscoll

QUESTION 5: Do molecular markers have a role in the diagnosis of elbow periprosthetic joint infection (PJI)?

RECOMMENDATION: Despite the presence of data related to the use of molecular markers for the diagnosis of infection in hip and knee arthroplasty, the role of molecular markers in the diagnosis of total elbow arthroplasty (TEA) infection remains unknown.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

An extensive literature search was performed to identify publications related to the use of molecular techniques for the diagnosis of PJI in TEA. Our detailed search revealed numerous articles in total hip and knee arthroplasty. From our search, 180 articles were ultimately reviewed. A complete search of the abstracts, references and selectively full text from systematic reviews specific to TEA revealed there were only three studies with a total of only three elbows examining the use of molecular techniques to diagnose periprosthetic infection in TEA.

The alpha-defensin immunoassay and leukocyte esterase (LE) tests were recently reviewed in a systematic review and meta-analysis by Wyatt et al. [1]. In this review, six studies examined alpha defensin; however, no TEAs were included. Five of the included studies utilized LE for the diagnosis of PJI and only one of these included a single TEA out of 52 prostheses examined [2]. In their study, Colvin at al. found a sensitivity, specificity, positive predictive value and negative predictive value of 100, 97, 95 and 100% respectively [2].

In another systematic review, Suen et al. [3] compared the "quick test" version of alpha-defensin to the laboratory-based test, which further led to a study by Sigmund et al. [4] which included hip, knee, shoulder and elbow revisions done for pain or instability in 49 patients. These authors found a sensitivity and specificity of 69% and 94%, respectively, with a positive and negative likelihood ratio of 12.46 and 0.33, respectively. Again, unfortunately this study only included a single patient with an elbow arthroplasty PJI. The larger systematic review found a pooled

sensitivity and specificity of the laboratory assay to be 95 and 96% respectively, compared to the quick test lateral flow of 77 and 91%, respectively, but again, only a single elbow arthroplasty was included in the pooled group.

Finally, in a pilot study by Wouthuyzen-Bakker et al., synovial calprotectin was examined as a biomarker for PJI [5]. This test is attractive because of the low cost, the possibility to obtain a quantitative value, the use of a lateral flow assay with the possibility to use it as a point of care test and its availability, as it is already used in routine care for other indications in most hospitals. Unfortunately, while this study included TEA, no PJIs were included in the TEA group. The single elbow examined was in a control group without infection. This pilot study revealed that synovial calprotectin had an overall sensitivity, specificity, positive predictive value and negative predictive value of 89%, 90%, 81% and 95%, respectively.

Other biomarkers examined in a pooled meta-analysis by Lee et al. [6] included α-defensin, LE, interleukin (IL)-6 and IL-8. The overall sensitivity of these molecular tests was 85% compared to culture, which was 80%. Alpha-defensin in this study had the highest diagnostic odds ratio. Unfortunately, all studies included hip and knee arthroplasties and not a single study examined TEA.

Of significant note, despite their ability to identify PJIs with a high likelihood in most other joints, all biomarkers utilized in these studies require some element of polymorphonuclear cells to be present in the synovial fluid for detection. These tests do not discriminate between other inflammatory conditions and infection, which would be the most useful to surgeons. Specifically, as inflammatory conditions have historically been the primary indication for surgical intervention about the elbow, a test to discriminate between infection and other inflammatory conditions such as rheumatoid arthritis or gout does not yet exist.

Nevertheless, as these tests have shown promise in PJI in other joints, studies should be undertaken specific to the elbow. However, at this time conclusions are difficult to draw given the lack of clinical data specific to the elbow, which forms the basis of our recommendation.

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Authors: Jonathan Barlow, Joaquin Sanchez-Sotelo

QUESTION 6: What are the diagnostic criteria for elbow periprosthetic joint infection (PJI)? (Clinical criteria, radiographic criteria, intraoperative findings, pathology, cultures and serum biomarkers.)

RECOMMENDATION: The following three parameters provide a definitive diagnosis of elbow PJI:

- A sinus tract that is communicating with the prosthesis (Strength: Strong)
- Isolation of identical pathogens from two or more separate cultures (tissue or articular fluid) obtained under sterile conditions (Strength: Strong)
- Presence of intra-articular pus (Strength: Consensus)

The following criteria are concerning for infection and should be considered in aggregate (Strength: Limited):

- Warmth, redness, swelling of the elbow
- Elevated serum inflammatory markers (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)) – except in cases of inflammatory arthropathies
- Elevated synovial white blood cell (WBC) count
- Elevated synovial polymorphonuclear percentage
- Isolation of organism from one sample (tissue or articular fluid)
- Histologic evidence of acute inflammation
- Early unexpected component loosening
- Endosteal scalloping, rapid progressive loosening on radiographs

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 92%, Disagree: 8%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

The limited total number of total elbow arthroplasty (TEA) infections reported in the literature makes the assessment of preoperative factors consistent with infection challenging. In addition, limited early recognition of the role of low-grade, indolent infections (*Staph-*

ylococcus epidermidis, Cutibacterium acnes) may make interpretation of earlier studies challenging. Nonetheless, the literature provides valuable insights into the diagnosis of PJI in TEA.

Given the subcutaneous nature of the elbow, many infected TEAs do develop draining sinuses. This diagnostic criteria has been consistently used in the literature and was predictive of positive cultures in the vast majority of cases. In the review by Cheung et al. of 29 patients with PJI, 11 (38%) had draining sinuses [1]. Peach et al. showed a 38% rate of draining sinus, as well [2].

Culture growth was the most commonly-cited diagnostic criteria in the literature. Several studies considered a TEA to be infected in the presence of one positive culture [1,3–9]. Several other studies only made the diagnosis of PJI if two cultures were positive for the same pathogen [10–12]. The latter is consistent with the MusculoSkeletal Infection Society (MSIS) criteria [13]. In light of the publication by Wee et al. regarding "unexpected positive cultures," using the criteria of one positive culture for the diagnosis in the absence of other signs would likely over-diagnose PJI [14]. Therefore, one positive culture should be used in the constellation of other signs and symptoms of infection. If two cultures from two separate sources return the same pathogen, the diagnosis of PJI is supported strongly by the literature.

Numerous other criteria were used in the diagnosis of PJI. While these signs and symptoms were frequently seen, they were not seen with enough reproducibility to be diagnostic in isolation. Warmth, redness and swelling were consistently seen [15]. Elevated serum ESR and CRP, as well as aspirate WBC (and differential), and acute inflammation on intraoperative pathology were commonly seen in TEA PJI. However, many of the patients receiving a TEA have inflammatory arthropathy as their underlying diagnosis, leading to a substantial number of false positives. Furthermore, in the setting of low-grade infections, aspiration and serum laboratory studies are not accurate in isolation. These diagnostic criteria should be used in combination with clinical and radiographic assessments to assess likelihood of true PJI.

The radiographic appearance of the TEA and pace of loosening can provide insight into the likelihood of PJI. Early unexpected radiographic failures (< two years) are more likely to be consistent with PJI than late failures [14,16]. In addition, endosteal scalloping and rapidly progressive loosening were associated with PJI in TEA in most series in the literature [4,9,15].

Based on available literature, it is hard to make consensus quantitative assessments of number of criteria required from the "associated criteria" category. Certainly, based on the literature, an increase in the number of positive criteria increases the likelihood of true PJI.

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Treatment

Authors: Mark Cohen, Robert N. Hotchkiss

QUESTION 1: Is there a role for irrigation and debridement with implant retention when treating acute elbow periprosthetic joint infection (PJI)? Should modular implant parts be exchanged?

RECOMMENDATION: Surgical debridement, antibiotic and implant retention (DAIR) is a viable option for management of acute elbow PJI. Modular implant exchange should be considered.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Total elbow arthroplasty (TEA) has historically been associated with a high risk of PJI. In 1983, Morrey et al. described this association and recommended the use of antibiotic-impregnated cement to reduce the risk of PJI after primary TEA [1]. Although infection rates have improved since then, PJI remains a potentially catastrophic complication of TEA. TEA implant revision is technically challenging, particularly given the relative lack of progress that has been made in TEA implant revision systems over the past 30 years. No comparative study exists to discern the superiority of DAIR versus explantation. Both strategies have been described, with varying degrees of success for both options [1–6].

Of the studies available for review, treatment recommendations varied. Given the variation in patient age and general health, bacteriology, mechanical circumstances, soft-tissue coverage and the retrospective nature of the study designs, it is difficult to make definitive recommendations about the indications for irrigation and debridement with retention of components. Alternative options include removal and reimplantation of new components in a single-stage or two-stage exchange with interval antibiotic cement spacer and resection arthroplasty.

Although no studies exist comparing DAIR with more invasive options, some patients do respond well to isolated irrigation and debridement [5]. There is extensive data to support the role of DAIR in the hip and knee arthroplasty literature. Because TEA systems rely on cement mantle fixation, explantation of well-fixed components leads to significant bone loss and morbidity.

Thus, DAIR may be offered to patients with infection of TEA in the presence of well-fixed components. The following general rules may need to be obeyed in performing DAIR in these patients.

1. If the components are well-fixed, removal of these implants will cause damage to the humerus and ulna, making the revision more challenging. Therefore, all attempts should be made to retain these using repeated irrigation and debridement, oral antibiotic suppression and soft-tissue coverage, even if that includes free tissue transfer.
2. If one component is found to be loose during DAIR, then the well-fixed component may be left in place while exchanging the other component.
3. In the presence of both components being loose, both components (and as much of the cement as possible) should be removed. An antibiotic-impregnated cement may be inserted with intravenous antibiotic treatment. The culture results would then dictate the length, dose and the type of antibiotic therapy needed.

Because resection arthroplasty leads to poor patient-reported outcome scores [6], we recommend that this option be reserved as a final "salvage" option after all other methods have failed or when the patient is not medically stable for two-stage exchange. Given the technical ease and low morbidity, we recommend that any modular components be removed and replaced in every case.

It is important to note that the method by which DAIR is performed influences the outcome of this surgical procedure. It is strongly recommended that clear margins for debridement of infected tissues are obtained, the modular components are taken out, the infected joint is irrigated copiously with antiseptic agents such as dilute betadine and the new modular parts are inserted after new drapes are used.

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QUESTION 2: What are the indications for one-stage and two-stage exchange arthroplasty when treating an acute or chronic elbow periprosthetic joint infection (PJI)?

RECOMMENDATION: Two-stage exchange arthroplasty should be considered for patients with chronic elbow PJI. There are no clear indications for one-stage exchange arthroplasty for infected total elbow arthroplasty (TEA), but two-stage exchange is preferred in patients with sinus tract and/or compromised soft tissues around the elbow or those with systemic sepsis.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Treatment strategies for elbow PJI have generally taken four forms: debridement, antibiotic and implant retention (DAIR), one-stage exchange arthroplasty, two-stage exchange arthroplasty, and resection arthroplasty. While DAIR is reported to be successful, this discussion will focus on staged reconstruction [1,2].

The body of evidence to support one-stage exchange arthroplasty is very sparse, with only one retrospective case series reported in the literature. Gille et al. reported on six infected TEAs treated with one-stage exchange arthroplasty. The outcome was successful in five patients, with a follow-up period ranging from 6 months to 16 years. Outcomes indicated patient satisfaction in four of six patients and a mean Mayo Elbow Performance Score of 67 points [3].

The evidence for two-stage exchange arthroplasty is greater than for one-stage, but is also limited to retrospective case series (level IV evidence). In an initial report, Wolfe et al. performed successful two-stage exchange arthroplasty on one elbow in their series of 12 elbow PJIs [4]. Yamaguchi et al. reported successful treatment in four out of five patients with infected TEAs [5]. In a follow-up study of an expanded patient cohort, Cheung et al. found a 28% reinfection rate with two-stage exchange arthroplasty [6]. Finally, Peach et al. studied 26 elbows undergoing two-stage exchange arthroplasty and reported successful eradication in 23 patients (88%) [7]. Pooling of the data on two-stage exchange arthroplasty from the literature results in 59 unique patients with an 18% recurrence rate.

Many of the studies regarding treatment of infected TEAs include a mix of acute and chronic infections with a wide range of surgical treatments and antibiotic regimens. In the setting of acute infection with early diagnosis, some authors recommend DAIR [8,9]. Most of these studies emphasize the importance of sufficiently robust patient health, an adequate soft tissue envelope, a sensitive organism and use of local intra-articular antibiotic placement in addition to intravenous therapy. In particular, debilitated patients may be treated with chronic antibiotic suppression if they are not able to tolerate the proposed surgical course, while intractable infections or inadequate soft tissue sleeves can be managed with resection arthroplasty [2,10].

There are no studies comparing one-stage and two-stage exchange TEA in similar patient populations. Achermann et al. studied 27 elbow PJIs, but most were treated by DAIR. In this series, one patient with a delayed infection was treated with one-stage exchange and two late infections with two-stage exchange arthroplasty. All three patients in this series had successful eradication of infection [9]. Spormann et al. reported on three late (> 24 months) and one acute (< three months) elbow PJIs treated with two-stage reconstruction (all were cleared of infection). Similarly, a one-stage exchange was used in one patient with a delayed (3 to 24-month) TEA infection, which was also successful [8]. Finally, in a review article Somerson et al. found inadequate data to recommend one-stage reconstruction, but reviewed the relative success of two-stage exchange arthroplasty with eradication of infection in 72-88% of patients [10].

Given the paucity of data surrounding one-stage exchange elbow arthroplasty, it is difficult to recommend an indication for this approach in the setting of elbow PJI. Though evidence overall remains limited regarding two-stage exchange, we conclude that this approach is currently favored for the treatment of acute and chronic infected TEA.

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QUESTION 3: Is there a role for preoperative joint aspiration prior to second-stage revision after treatment of elbow periprosthetic joint infection (PJI)?

RECOMMENDATION: Preoperative joint aspiration may play a role in the evaluation of the elbow arthroplasty for PJI before second-stage revision.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 96%, Disagree: 0%, Abstain: 4% (Unanimous, Strongest Consensus)

RATIONALE

There are no studies that specifically investigate and prove that there is a role for preoperative aspiration of the elbow prior to second-stage revision arthroplasty. However, in a review of published studies that have addressed total elbow infection, aspiration was found to be the standard of practice in these studies. Furthermore, there is a logical rationale that preoperative aspiration provides useful information for both the diagnosis and treatment of total elbow arthroplasty (TEA) infections. When the risk factors for infection are higher (such as in patients with diabetes, obesity or rheumatoid arthritis), preoperative aspiration prior to second-stage revision has an even stronger recommendation. Currently, no evidence exists regarding what constitutes a positive aspiration. Therefore, the significance of the results should be assessed on a case-by-case basis.

Rudge et al. discussed the management of infected elbow arthroplasty by two-stage revision in 19 patients managed at their center [1]. In their algorithm for management, the authors state, "If the infective organism and sensitivities had been identified before the first stage, further antibiotics were added as necessary. If at the six-week postoperative review there were clinical signs of ongoing infection or inflammatory markers had not normalized, an aspiration was performed. If the aspirate analysis was positive, then patients underwent a repeat first-stage procedure (debridement and washout). If the aspirate analysis was negative, then a second-stage procedure was planned, but with a low threshold for making an intraoperative decision to repeat the first stage rather than re-implanting prosthetic components, if concerned about possible ongoing infection." These authors therefore recommend aspiration prior to second-stage revision as a means of determining when to proceed to the second stage, what procedure to perform and which antibiotics to use.

Using this protocol, the authors were able to treat the majority of TEA infections successfully — "Of the 19 patients undergoing a first-stage procedure, 16 (84%) remained infection free, of whom 11 had proceeded to a second stage and five had not. Of 14 patients undergoing a two-stage revision, 11 (79%) remained infection free. Of patients requiring further surgery due to recurrent infection, 2 (67%) remained infection free after a repeat two-stage revision, with the third patient still awaiting the second-stage procedure."

When aspiration is performed, the joint fluid should be evaluated for white blood cell (WBC) count, with particular attention to the differential (polymorphonuclear percentage). In addition, the fluid should be sent for aerobic and anaerobic cultures. Gram stains lack sensitivity and specificity and are not routinely recommended [2,3]. Cultures remain the most effective method for specific organism identification. The addition of Acid-Fast Bacilli (AFB) and fungal cultures should be performed if there is concern for atypical infecting organisms. Additionally, incubating cultures for a longer period (21 days) may assist in identifying fastidious organisms such as *Cutibacterium acnes*.

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QUESTION 4: What is the role of permanent resection when treating a chronic elbow periprosthetic joint infection (PJI)?

RECOMMENDATION: Permanent resection is a salvage treatment for chronic elbow PJI. Preservation of medial and lateral condyles should be considered to improve functional outcomes.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Methodology

A comprehensive literature review was performed to identify all studies on permanent resection treatment for elbow PJI. Searches for the terms "elbow," "total elbow arthroplasty," "infection," "periprosthetic," "permanent resection" and "resection arthroplasty" were performed on the PubMed/Medline, Cochrane, Google Scholar and Embase databases through March of 2018. Our systematic review includes English studies (only level IV evidence) regarding permanent resection treatment for the elbow PJI. Non-English studies, technique papers without patient data, studies with inadequate patient follow-up and studies regarding resection treatment for non-elbow PJI were not included. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement was followed for this review.

Discussion

PJI is a serious complication of total elbow arthroplasty (TEA) and is difficult to treat [1,2]. Treatment options include debridement with retention of implants, single or two-stage reimplantation, permanent resection and arthrodesis [1–5]. There are only a few studies with limited evidence comparing the outcomes of these treatment procedures [3–7]. Many authors have emphasized that good functional outcomes are only possible with reimplantation [8,9]. However, the success of the reimplantation treatment depends on remaining bone stock [9,10]. On the other hand, high recurrence rates of infection limits the success of the treatment [8]. Arthrodesis and permanent resection are defined as a salvage procedure in low-demand patients [1,2,5,7]. However, arthrodesis has a very limited role in the treatment of this circumstance, even as a salvage treatment, as it often results in a painful nonunion or infection recurrence [3].

Permanent resection is suggested as a salvage procedure for the treatment of elbow PJI in patients in whom debridement and reimplantation therapy had failed or in medically frail patients [2,7]. Rhee et al. reported that infections in nine patients (90%) could be eradicated with permanent resection for elbow PJI [11]. Despite the high successes of eradication of the infection, it was noted that sufficient stability was essential for the successful functional outcomes. It was emphasized that the condyles which articulate with the olecranon fossa are important for the stability in resection arthroplasty. Moreover, the authors have examined the role of poor bone stock in the condyles (which is common in this patient group) on the success of resection arthroplasty. It has been reported that the best functional results were obtained in patients in whom both condyles could be preserved, whereas the weakest functional results were reported to be obtained in the group of patients in whom only the medial condyle could be preserved. Figgie et al. reported that achieving stability has a key role in the success of resection arthroplasty following failed TEA [12]. Therefore, the authors emphasized that the epicondyles should be preserved.

In a study by Zarkadas et al., resection arthroplasty has been defined as an effective salvage procedure [1]. This study appears to be noteworthy due to fact that it reported the long-term outcomes of 29 patients (30 elbows) after resection arthroplasty for the failed TEA (11 years, range 2.7 to 28 years). In the study, it was noted that the increase in the Mayo Elbow Performance Score was reported to be mostly in the pain component, whereas the stability was directly related to good functional outcomes. However, the authors reported complications such as persistent infection in 24 elbows (47%), intraoperative fracture in 18 elbows (35%) and permanent nerve injury in 9 elbows (18%).

Specifically, the difficulties experienced during removal of the well-fixed humeral component were thought to be responsible for the high complication rates. For this reason, the authors suggested performing an osteotomy in the form of a trapezoidal window, which has a larger distal border in order to facilitate removal of the humeral component and cement. In addition, the authors pointed to the importance of the development of soft tissue scar utilizing a brace or a cast for a minimum of six weeks to surpass instability, which is thought to be responsible for the poor functional outcomes.

PJI following an elbow arthroplasty has a reported rate ranging from 22 to 41%, based on limited literature [1,2]. Diagnosis of chronic elbow PJI has remained a challenge, however, as many presentations are subclinical in nature, leaving cultures still as the recommended diagnostic tool [3]. Treatment of elbow PJI has primarily centered on intravenous antibiotics, debridement and retention as well as staged reimplantation, all of which have been proven to be relatively successful under the right indications [3–5]. There is limited literature regarding the success of this treatment modality. Permanent resection may be considered if previous attempts to resolve elbow PJI fail [3,6,7]. Zarkadas et al. found that 47% of their case series required additional surgery after permanent resection to resolve the infection [6].

There are no level I or II studies available, though one level III and two level IV studies exist examining permanent resection as a treatment modality for chronic TEA PJI. Both level IV studies are case series with sample sizes of 51 and 10 patients, respectively [3,7]. Both level IV studies demonstrated that successful eradication of PJI is heavily dependent on surgical technique and more experienced TEA surgeons are correlated with higher eradication rates for elbow PJI via permanent resection.

One study reported patient outcomes and showed higher functional Disabilities of the American Shoulder and Hand scores with resolution of elbow PJI via permanent resection [6]. Therefore, even with the paucity of literature available, permanent resection should be considered for chronic elbow PJI that fails to respond to other treatment modalities.

In brief, the permanent resection has been suggested for frail patients with low functional demands or for patients who are not interested in additional reconstructive surgeries [1,2,7,11]. The aim of treatment should be the eradication of infection, relief of pain and improved functions [1,4,11]. Contrary to what is known, persistent infection is a frequent complication [8]. Given this finding, all of the infected tissue and foreign materials should be removed [1,7,11,12]. However, aggressive debridement and removal of the well-fixed implants result in loss of bone stock [1,11]. This condition increases the instability risk which is directly correlated with poor functional outcomes [1]. Both condyles should be preserved as much as possible so that a new effective fulcrum might be created, which would make it possible to achieve a stable new elbow joint [8,9,11]. In order to achieve favorable functional outcomes and soft tissue stability, the integrity of the triceps mechanism should be preserved [12] and immobilization should be ensured for a minimum of six weeks postoperatively by casting or bracing [1].

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QUESTION 5: What is the role of arthrodesis when treating a chronic elbow periprosthetic joint infection (PJI)?

RECOMMENDATION: There is a very limited role for arthrodesis of an infected elbow, as this procedure usually results in painful nonunion and poor functional outcomes.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The incidence of deep infection after total elbow arthroplasty (TEA) has been reported to be 3–13.3% [1–4]. It has been widely accepted that elbow PJI is difficult to treat and has poor outcomes [1,2,5]. Compared to knee and hip arthroplasties, relatively high infection rates [2] and poor outcomes [6] have led to an assessment of the efficacy of different treatment procedures [2,5]. Treatment modalities include debridement with prosthetic retention, resection with subsequently staged reimplantation, staged reconstruction with composite allograft, permanent resection and arthrodesis [2–9].

Among the aforementioned treatment modalities, arthrodesis must be the last choice and should be regarded as a salvage procedure. Functional limitation after arthrodesis cannot be compensated by adjacent joints [8,10,11]. Small contact areas of the remaining bone stock and high moments generated by the long lever arm preclude obtaining solid bone fusion [8,11,12]. Even if fusion can be achieved, it has been reported that humerus fracture risk increases in longer follow-up [13]. Arthrodesis has been reported to be a successful treatment only if there is adequate bone stock, good soft tissue envelope and sufficient vascular supply [8,14,15]. However, in majority of patients with elbow PJI, there are bone defects due to the destructive effect of infection, removal of bone as part of treatment of infection, vascularity is impaired and soft tissue coverage may be insufficient secondary to recurrent surgical interventions [2,5,12–16].

Wolfe et al. described two patients treated with arthrodesis after elbow PJI [9]. The authors reported a painful fibrous union in one patient and a persistent infection in the other. In the limited literature evaluating the treatment of arthrodesis after elbow PJI, the largest series (by Otto et al.) consists of five patients [11]. The authors reported that no union was achieved in any of the patients, and there was asymptomatic fibrous union in only two patients (40%) at the last follow-up. In that study, high reoperation rates and high complication rates were emphasized, and arthrodesis was not recommended for the elbow PJI.

Severe bone loss in this patient group was seen as an important cause of treatment failure. Thus, Koller et al. described an arthrodesis technique using double fibular strut graft and reported favorable results in a patient at the 12-month follow-up [10]. The arthrodesis of the radius to the humerus described by Presnal et al. aimed to surpass nonunion caused by the massive bone loss in the ulna [8]. Nevertheless, according to widely accepted view, arthrodesis treatments for the elbow PJI have poor outcomes and high reoperation rates, and it is not recommended except in special conditions [4,9,14–18]. It might be considered in the case of a failure of resection arthroplasty due to instability [15,17], especially when control of sepsis due to the mobility of the articulation is not possible [14] and also in young patients who do heavy bodily work [18]. Because of the limited literature and small case series, the role of arthrodesis in the treatment of elbow PJI could be evaluated with a limited level of strength.

Treatment of elbow PJI has centered on antibiotics, surgical debridement and retention or staged reimplantation [1]. In some cases where the joint is extremely damaged or seems unsalvageable, arthrodesis may be a viable treatment choice to avoid amputation [1]. Traditionally arthrodesis of the elbow has only been used when all other motion-preserving interventions are declared not possible and studies have reported elbow arthrodesis results in more impairment than hip, knee or ankle joint arthrodesis [2,3]. Koch and Lipscomb report that arthrodesis should be considered only when there is sufficient tissue damage to prevent reimplantation following TEA PJI, and in these cases they reported a 15% delayed complication rate [13].

Literature examining the success of elbow arthrodesis for chronic PJI is limited. There have been no level I, II or III studies, and only two level IV studies have examined the use of arthrodesis for chronic elbow PJI related to tuberculosis [5,6]. A recent review article suggested that evidence to support the use of arthrodesis is

incomplete as a treatment modality for chronic elbow PJI [11]. One aspect that should be taken into account is the technique used during arthrodesis, as Sala et al. found this influences the functional outcome following elbow PJI [19]. Overall, due to the limited literature, we cannot recommend the use of elbow arthrodesis to treat chronic elbow PJI.

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QUESTION 6: Should all foreign material (including cement) be removed during resection arthroplasty of an infected elbow?

RECOMMENDATION: When treating elbow periprosthetic joint infection (PJI), attempts should be made to remove all foreign material. However, the benefit of removing all foreign material should be weighed against the effort to preserve bone stock.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Surgical management of an infected total elbow arthroplasty (TEA) is dependent on the chronicity of the infection and the infecting organism, as well as host factors. The majority of TEA components are placed in a cemented fashion. In cases where the humeral and ulnar components are removed, the cement mantle may or may not be easily extractable at the time of surgery. This discussion will focus on the literature which reports on patient outcomes following TEA component resection with retained foreign material.

A systematic review was performed using the search terms, "retained cement AND total elbow arthroplasty NOT shoulder." This search yielded zero results. Therefore, a broader search criterion was utilized. The second search evaluated "total elbow arthroplasty AND infection AND removal NOT shoulder." All 32 articles were reviewed. Of these, only one paper documented retained cement in the setting of removal of the humeral and ulnar components. Stoodley et al. [1] reported a single case series of a TEA performed for a distal humerus fracture nonunion. The patient underwent multiple staged operations including before and after the index TEA. Cultures remained negative until the seventh operation, when the authors noted a positive culture and documented that retained cement was removed at that time. However, the authors were unable to state if the retained cement was the cause of persistent infection, as the patient had not previously received targeted antibiotics that effectively addressed the infectious antimicrobial profile.

Given the lack of evidence available within the total elbow arthroplasty literature, information regarding the effect of retained cement must be taken from other orthopaedic literature. Early reports in the lower extremity arthroplasty literature raised concern about the correlation of retained cement and incomplete eradication of infection [2]. However, not all series have correlated retained cement with persistence of infection [3,4]. Petty et al. reported on 54 total hips treated for PJI. At the time of revision surgery, the presence of retained cement was not associated with positive intraoperative cultures.

Given the lack of data available in the elbow arthroplasty literature, we are unable to make a recommendation regarding the necessity to remove all cement or other foreign material in the treatment of periprosthetic TEA infections.

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QUESTION 7: Is there a role for chronic antibiotic suppression in the management of elbow periprosthetic joint infection (PJI)?

RECOMMENDATION: Long-term suppressive antibiotics may be used in the treatment of PJI of the elbow. Consultation with an infectious disease specialist should be considered in the decision to use long-term suppressive antibiotics.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Treatment strategies for elbow PJI have generally taken four forms; irrigation and debridement with component retention, one-stage exchange arthroplasty, two-stage exchange arthroplasty and resection arthroplasty. Each of these treatment options may be followed by the use of suppressive antibiotics [1].

A systematic review was performed using the terms "elbow arthroplasty AND chronic suppressive antibiotics." This revealed zero results. A second search using the terms "infected elbow replacement AND suppressive antibiotics" produced no results. A third search using the terms "infected elbow AND chronic suppressive antibiotics" produced zero results.

A fourth search using the terms "chronic suppressive antibiotics AND elbow infection" produced a single result: "Gram-Negative Prosthetic Joint Infection: Outcome of a Debridement, Antibiotics and Implant Retention Approach. A Large Multicentre Study" [1]. In this multi-center study from Spain, there were two elbow PJIs out of 242 PJIs managed with debridement and chronic suppressive antibiotics (the other 240 patients included 150 hip, 85 knee and 5 shoulder). They reported 79% successful outcomes. Ciprofloxin exhibited a protective effect and chronic renal impairment predicted failure.

A final search with the terms "chronic suppressive antibiotics AND total joint infection" produced 12 results. Only one study (the previously-cited Rodriguez-Pardo article) included elbow replacement patients. Given the lack of evidence specific to PJI of the elbow, the only evidence available is contained in articles related to PJI of other joints. Aboltins et al. published a review citing a 77% success rate using rifampin-based therapy [2]. These two articles provide the most recent evidence in the use of antibiotic suppression in the treatment of PJI of the elbow. There are several other articles, primarily on hip and knee, and two are referenced that provide further evidence in support of suppressive antibiotic therapy [3,4].

In the absence of concrete data and given the complexity of removing well-fixed cemented components of total elbow arthroplasty, we believe suppressive antibiotic therapy may have more of an expanded role in these patients than in PJI affecting other joints.

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PART VI

FOOT AND ANKLE

Prevention

1.1. PREVENTION: TOTAL ANKLE ARTHROPLASTY-SPECIFIC

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QUESTION 1: What are the important risk factors that predispose a patient to infection after total ankle arthroplasty (TAA)?

RECOMMENDATION: There is evidence indicating that the following risk factors may predispose a patient to an infection after a TAA: inflammatory arthritis, prior ankle surgery, body mass index (BMI) < 19 and peripheral vascular disease. Meanwhile, there is conflicting evidence (which may be due to patient selection bias) indicating that the following risk factors may predispose a patient to infection after a TAA: obesity (BMI > 30), tobacco use, diabetes, duration of surgery, age < 65 years, hypothyroidism, low preoperative American Orthopaedic Foot and Ankle Society (AOFAS) hindfoot score and chronic lung disease.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE:

The purpose of TAA is to eliminate pain while restoring some functional range of motion. One of the dreaded complications of TAA is a periprosthetic joint infection (PJI). The reported rate of this complication ranges between 0-8.9% [1–4]. Appropriate patient selection could be facilitated by understanding the preoperative risk factors for PJI.

Inflammatory arthritis is one of the patient characteristics that have been identified by two separate studies as a risk factor for PJI. In a retrospective comparative series, Raikin et al. followed 106 patients who had undergone a TAA and identified nine patients who necessitated a return to the operating room for an irrigation and debridement and/or removal of their hardware [5]. The authors concluded that an underlying diagnosis of inflammatory arthritis was a significant risk factor leading to the complications studied. Of note, patients with inflammatory arthritis showed a 14.03-times increased risk of requiring reoperation. Althoff et al. reached a similar conclusion in a database comparative study [6]. The authors used a national insurance database to select 6,977 TAA patients and assess which factors correlated with an increased risk of PJI within the first 6 postoperative months. Several risk factors were highlighted, one of which was a diagnosis of inflammatory arthritis.

A history of prior ankle surgery has been identified as a risk factor for PJI. Patton et al. retrospectively reviewed the cases of 966 patients who had a TAA and found 29 instances of postoperative infection [7]. Prior surgery of the ankle was found to correlate with an increased risk of PJI. In a comparative cohort study, Kessler et al. evaluated 26 demographically matched patients who developed PJI, the authors concluded that prior ankle surgery increased the risk of infection [1].

Age < 65 years (odds ratio (OR) 1.61), a BMI < 19 (OR 2.67), peripheral vascular disease (OR 2.46), chronic lung disease (OR 1.51) and hypothyroidism (OR 1.32) were all determined to be a risk factor for PJI following TAA in a single study [6]. Low preoperative AOFAS hindfoot scores were also identified as a risk factor by a single study [1]. These findings, however, have not been corroborated by other publications.

There is conflicting evidence in the literature regarding the role of obesity in TAA. A single database study identified a BMI > 30 as a risk factor for developing PJI [6]. This, however, is contradicted by two separate retrospective comparative series. Schipper et al. assessed the outcomes between 49 obese patients and 48 non-obese patients following TAA [8]. While the authors noted that there was decreased survivorship of the implant in the obese patient population, there was no increased risk of infection. Similar findings were noted in a large case series comparing patient-related factors between TAAs that developed infection and those that did not [7].

Whether tobacco use is a risk factor for PJI is not clear based on the current literature. The database publication by Althoff et al. concluded that smoking increases the risk of a PJI (OR 1.59) [6]. Lampley et al. compared the postoperative outcomes between nonsmokers (n = 359), former smokers (n = 249) and current smokers (n = 34) [9]. The authors concluded that while the active smokers had an increased rate of PJI, this did not reach statistical significance. Patton et al. however, concluded in their large case series that there was no association between tobacco use and postoperative infection following TAA [7].

The current literature is divided on the issue of whether diabetes is considered a risk factor for PJI [6–8,10]. The publications by Althoff et al. [6] and Patton et al. [7] both conclude that diabetic patients are at increased risk of infection. Further, Schipper et al. reached a similar conclusion that diabetes was an independent risk factor [9]. However, Gross et al. assessed the complication rate between 50 diabetic patients and a control group and concluded that diabetes did not increase the risk of infection [10]. Additionally, the length of the operative procedure is a risk factor that has shown some variance in the literature. Kessler et al. reported that the duration of the surgery was significantly longer (119 minutes) in the infected group, compared to the age and sex-matched control group (84 minutes) [1]. In contrast, Patton et al. found no difference in operative times between patients who developed a PJI and those who did not [7].

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QUESTION 2: Does intra-articular injection of the ankle with corticosteroids increase the risk of subsequent periprosthetic joint infection (PJI) following total ankle arthroplasty (TAA)? If so, how long after a prior intra-articular injection can TAA be safely performed?

RECOMMENDATION: Every intra-articular injection of the ankle is an invasive procedure associated with potential healthcare-associated infections, including periprosthetic joint infection (PJI) following TAA. Based on the limited current literature, the ideal timing for elective TAA after corticosteroid injection for the symptomatic native ankle joint is unknown. The consensus workgroup recommends that at least three months pass after corticosteroid injection and prior to performing TAA.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 8%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

Intra-articular steroid injections may transiently relieve the pain of osteoarthritis of the ankle and are widely used for its treatment. At the same time, every injection is an invasive procedure and might be associated with health-care-associated infections, including PJI following TAA. Seror et al. noted that the risk of septic arthritis after an intra-articular steroid injection is 1 in 70,000 [1]. For native ankle joints, one study found a 3.9% infection risk when using intraoperative steroids versus a 1.8% infection risk when performing arthroscopy without steroids [2]. However, this study was not related to TAA, and many other studies in native ankle joint arthritis deny a relationship with steroid injections.

The available literature investigating the effect of intra-articular corticosteroid injections on postoperative PJI are all in hip and knee arthroplasty patients. Some studies find no relationship between corticosteroid injections and infection [3–6], while others find an increased risk of deep infection following intra-articular injection [7–11]. Studies that find a positive correlation also suggest that timing may be an important factor, and that injections more closely preceding surgery may lead to an even higher risk of infection.

Unfortunately, there are no published data in regards to the risk of PJI after steroid injection in the setting of TAA. The data from hip and knee arthroplasty may not be applicable to TAA, and further studies are warranted.

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Authors: Jonathan Kaplan, Gaston Slullitel, Valeria Lopez

QUESTION 3: Should routine methicillin-resistant *Staphylococcus aureus* (*S. aureus*), or MRSA, screening be in place prior to total ankle arthroplasty (TAA)?

RECOMMENDATION: Unknown. The role of screening for MRSA and decolonization prior to TAA remains unclear. Further data is needed to support this practice in TAA, which can be costly and logistically difficult to implement.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

There is growing concern about the increase of postoperative infections due to antibiotic-resistant organisms [1], and this is particularly important in orthopaedic surgery where the increasing incidence of antibiotic-resistant *Staphylococci* threatens the outcome of implant-related procedures. The complication rate and cost of periprosthetic joint infection (PJI) associated with MRSA is considerably higher compared to those associated with methicillin-sensitive *Staphylococcus aureus* (MSSA) [2]. Patients receiving orthopaedic implants are most vulnerable, given the potential for biofilm formation and long-term morbidity [3].

Furthermore, the prevalence of surgical site infections (SSIs) as a result of MRSA has increased over the last few years. Between 1992 and 2003, the prevalence of MRSA increased from 32% to 64% of all isolated nosocomial pathogens found on patients in hospital intensive care units (ICUs), representing a 3.1% increase in MRSA prevalence per year [4].

The last two decades have seen an increase in community-acquired MRSA (CA-MRSA), a subpopulation of MRSA with unique antibiotic resistance properties, high virulence characteristics and pathogenic capability. This subset of MRSA tends to affect young and otherwise healthy patients [5–7].

Several screening strategies have been studied in terms of their cost-effectiveness [8,9]. As the *S. aureus* strain isolated from SSIs commonly matches (in up to 85% of cases) the *S. aureus* strains sampled from the noses of colonized patients, nasal swabs emerge as a potentially cost-effective screening option [10–12].

However, the evidence is not conclusive regarding an association between rapid screening and the acquisition rate for MRSA or risk of MRSA-induced SSIs. However, in the setting of a positive result, it allows for the implementation of a decolonization protocol that is indeed effective in significantly reducing the rate of SSIs caused by MRSA [7].

A recently published, large multicenter prospective cohort trial by Schweizer et al. involving > 40,000 unique operations examined the effect of the introduction of a standardized preoperative *S. aureus* screening and decolonization program on deep *S. aureus* SSIs in cardiac surgery and hip and knee arthroplasties performed at 20 hospitals [13]. The authors reported that the hip and knee arthroplasty cohort demonstrated a significant reduction in postoperative rates of deep infection with *S. aureus* following the introduction of the screening and decolonization program.

Numerous studies have demonstrated that the most common pathogens in SSIs following total hip arthroplasty/total knee arthroplasty (THA/TKA) are MSSA and MRSA. Additionally, many of these studies have demonstrated that positive colonization correlates with increased SSIs and multiple studies have demonstrated the benefit of treating patients who test positive on preoperative screening. When assessing the cost-effectiveness of screening and decolonization, multiple studies have shown potential to substantially reduce the cost of THA/TKA by decreasing the rate of SSIs. Lastly, recent studies have demonstrated cost-effectiveness in universal decolonization programs with or without the inclusion of preoperative *S. aureus* screening. The latter has become a reality as numerous non-antibiotic agents have been introduced.

In the absence of concrete evidence supporting MRSA screening and decolonization in patients undergoing TAA, perhaps consideration should be given to universal decolonization of these patients using one of these non-antibiotic agents.

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QUESTION 4: What preoperative optimization should be implemented to reduce the risk of surgical site infection/periprosthetic joint infection (SSI/PJI) in patients undergoing total ankle arthroplasty (TAA)?

RECOMMENDATION: We recommend that patients awaiting TAA be optimized prior to surgery by implementing skin cleansing, nutritional status enhancement, glycemic control, body mass index (BMI) optimization, smoking cessation, and management of immune-modulating comorbidities.

At the time of surgery, there is strong evidence that optimal preparation of the surgical site with an alcohol-containing agent, weight-based and timely administration of antibiotic prophylaxis, and reducing operating room traffic should also be put in place.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RESPONSE

PJIs complicating total joint arthroplasty (TJA) are potentially catastrophic events to patients and immense financial burden to the healthcare system [1,2]. These events can occur intraoperatively, immediately postoperatively or as a late complication via direct or hematogenous spread of pathogens to the prosthetic joint. The prevention of this potentially serious complication should always be a priority, and this is best achieved by the implementation of proper preventive strategies. Though preoperative optimization prior to TAA is limited in the literature. We recommend utilizing similar methods proven to prevent infection after total knee and hip arthroplasty.

In an attempt to decrease SSIs caused by *Staphylococcus aureus* (*S. aureus*), or MRSA, Alexander et al. recommended the use of chlorhexidine footbaths in patients with nasal colonization of *S. aureus* beginning five days prior to their foot and ankle surgery in addition to standard operative disinfection protocols [3]. Colling et al. demonstrated that a preoperative antiseptic shower and bath policy was associated with a significant decrease in *S. aureus* and MRSA SSI [4]. Despite being a valid option in preventing *S. aureus* and MRSA infections, this shower and bath policy failed to achieve a decrease in the total incidence of SSI. Prior to the procedure, prophylactic antibiotics such as cefazolin can be administered to patients, as this is considered an essential part of the foundation of SSI prevention due to its long-accepted reduction of infection in orthopaedic procedures and a current recommendation from the American Academy of Orthopaedic Surgeons [5–7]. Interestingly, in their retrospective study comparing the use of antibiotic prophylaxis either 15-60 minutes or less than 15 minutes prior to foot and ankle surgeries, Tantigate et al. found that the timing of intravenous antibiotic prophylaxis did not play a significant role in the risk of developing SSI [5].

In addition to external preventative measures, optimizing the nutritional status of patients undergoing TAA to optimize the immune system is important. Several studies on infections following orthopaedic procedures have demonstrated that a lymphocyte count below 1,500 cells/mL, an albumin level below 3.5 g/dL, a zinc level below 5 mg/dL, and a transferrin level below 200 mg/dL have been associated with increased risks of infection and delayed wound healing [8–12]. Therefore, nutritional parameters should be measured in those suspected of being malnourished and the abnormal parameters corrected prior to elective arthroplasty.

The optimization of medical comorbidities should also be considered an essential part of the preoperative protocol aimed at reducing PJI following TAA. Marchant et al. reported that the current glycemic control of patients with diabetes mellitus (DM) is more important toward the risk of infection following TJA rather than the diagnosis of DM itself, as the risk of infection of diabetic patients with controlled glucose levels was the same as patients without DM [13]. In their study on total hip and knee arthroplasties, Mraovic et al. further concluded that blood glucose levels immediately prior to and after surgery were significantly correlated with subsequent infection risk. These authors reported that non-DM patients with blood glucose levels greater than 140 mg/dL on the morning following surgery had a three-fold increase in infection risk [14]. Therefore, proper glycemic control in all patients should be performed in order to decrease the risk of SSI and PJI.

As obesity has been consistently shown to be associated with SSI risk in total hip and knee arthroplasties, especially BMI > 30 kg/m^2, weight reduction strategies leading up to surgery as well as dose-based antibiotic prophylaxis immediately prior to surgery in obese patients should be performed [1,15,16].

Certain other comorbidities are also highly related to an increased risk of infection in TJA due to decreased patient immunity, and these should be taken into consideration prior to surgery [1]. In their investigation into patient-related risk factors for PJI following TAA, Althoff et al. reported that, in addition to DM and obesity, a BMI < 19 kg/m^2, tobacco use, inflammatory arthritis, peripheral vascular disease, chronic lung disease and hypothyroidism were independent risk factors for PJI development following TAA [17]. Therefore, smoking cessation and optimization of these other aforementioned medical comorbidities should be performed prior to surgery. In their discussion of infection reduction following TJA, Matar et al. recommends this optimization of patient health through a preoperative evaluation by an internal medicine consultant or cardiologist, who subsequently follows the patient throughout their hospital course and postoperative period [18].

In the period immediately prior to surgery and within the operating room, we recommend utilizing the specific measures reported by Illingworth et al. and Matar et al. regarding infection minimization in TJA [1,18]. Optimization through the assessment of the skin around the ankle for any irregularities, surgical site skin decontamination through alcohol and betadine solutions, surgical site shaving, planning of surgical incision path, and appropriate draping with plastic adhesive, iodine-impregnated drapes should be considered in order to reduce PJI following TAA [18,19]. In addition, implementation of intraoperative measures, such as reducing foot traffic, having an operating room with an efficient ventilation system to reduce aerosolized particles and performing the surgery in an expeditious manner, are all proven to reduce the risk for subsequent SSI/PJI [18, 20–25].

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QUESTION 5: What prophylactic antibiotic (type, dose and route of administration) should be administered perioperatively for patients undergoing total ankle arthroplasty (TAA)?

RECOMMENDATION: The administration of prophylactic antibiotics before TAA potentially reduces the incidence of surgical site infection (SSI) and/or periprosthetic joint infection (PJI). Weight-based (of at least 2 gm) Cefazolin administered intravenously within 60 minutes prior to the procedure can be an adequate choice for antibiotic prophylaxis.

If the patient has a beta-lactam anaphylaxis, we recommend an appropriate alternative antibiotic effective against *Staphylococcus*.

It is unclear whether prophylaxis should be given as a single dose or as multiple doses.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Published studies report a rate of PJI after TAA that ranges from 2 to 8.6%, exceeding the risk of infection following knee and total hip replacements [1]. Likewise, the incidence of SSI following foot and ankle elective surgeries (2-4.5%) is higher than other orthopaedic procedures [2].

Most expert panels consider it appropriate for antimicrobial prophylaxis to be routinely utilized in surgeries involving prosthetic joints [3–8]. Unfortunately, no high level evidence is available to corroborate its indication specifically in TAA [9,10].

Gram-positive cocci are the most prevalent pathogens in SSI and PJI in foot and ankle surgeries [1,5,11]. Cefazolin is the more widely used antibiotic for standard prophylaxis in orthopaedic surgeries, due to its effective and rapid bone and soft tissue penetration, excellent gram-positive coverage and its long half-life [12,13]. One to 2 grams of Cefazolin administered intravenously is the standard dosage recommended in most guidelines, although some experts suggest increasing the dose to 3 grams if the patient weighs more than 120 kilograms [3,4,7,12]. In patients with a history of severe beta-lactam allergy, who cannot receive cephalosporins, vancomycin or clindamycin are adequate alternatives [3,4,12].

Some studies show reduced SSI rates associated with methicillin-resistant *Staphylococcus aureus* (MRSA) screening and decolonization protocols in elective orthopaedic procedures, but there is no specific data in foot and ankle surgeries or TAA [14,15]. Most experts

recommend performing these procedures on a case-by-case basis, taking into account the history of colonization and the presence of risk factors for MRSA [10,15].

Most guidelines advocate for the administration of prophylactic antibiotics within 60 minutes prior to surgery [3,4,6,7,10]. Studies that assessed patterns of antibiotic bone penetration in prosthetic joint replacements report that effective serum levels of Cefazolin persisted for over eight hours after intravenous administration, achieving peak concentration in bone tissue 40 minutes after the dose [13]. Antibiotic administration 15 minutes prior to incision has not proven to be better than 15-60 minutes before the procedure [2]. Experts advise redosing if procedure time exceeds one to two times the half-life of the antibiotic (1.5-two hours in case of Cefazolin) [3,4,6]. There is conflicting evidence for the need to continue prophylaxis postoperatively, but it is clear that there is no benefit in extending the administration of antibiotics beyond 24 hours after the surgical procedure [4–7,10]. If a proximal tourniquet is used, the antimicrobial should be completely infused before inflation [10,13].

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QUESTION 6: What is the optimal management of patients with prior septic arthritis of the ankle who are undergoing total ankle arthroplasty (TAA)?

RECOMMENDATION: There is a paucity of data regarding TAA in patients with prior infection involving the ankle, whether it be septic arthritis, osteomyelitis or infection of the surrounding soft tissues.

We recommend that patients with prior infections in the affected ankle be worked up for infection, including a thorough history and physical examination, as well as ordering serological tests and possible aspiration of the joint. During ankle arthroplasty in patients with prior infection, antibiotics should be added to the cement (if used), and the joint should be thoroughly cleansed. Intraoperative cultures of bone and soft tissue should also be obtained.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

TAA has been used with increasing frequency for the treatment of end-stage arthritis of the ankle. The rate of periprosthetic joint infection (PJI) of the ankle varies in the literature. When it occurs, it can have devastating consequences. There is a paucity of literature regarding the work-up, management and outcomes of PJI in TAA.

With regards to total ankle arthroplasty in patients with a history of infection involving the ankle, only one study in the literature was identified and was a level IV case series. A history of infection in or around the ankle was traditionally seen as a relative, if not absolute, contraindication to TAA [1,2]. However, until 2015, there were no studies on the matter in the foot and ankle literature.

Shi et al. retrospectively identified 22 patients over a 7-year period who underwent TAA who had a history of septic arthritis of the ankle or periarticular osteomyelitis [3]. The preoperative workup for these patients differed based on clinical suspicion and the treating surgeon's preferences. At the very least, all patients had preoperative blood work in the form of a complete blood count (CBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. The decision to perform a preoperative joint aspiration or send intraoperative frozen sections or tissue samples for culture was surgeon-dependent.

At a mean follow-up of 29.3 (range, 11.4 to 83.8) months, there were no PJIs, evidence of radiographic loosening or need for revision of the components. The TAA was performed at an average of 8.8 (range, 0 to 44) years after the diagnosis of infection in or around the ankle. Three patients (14%) had delayed wound healing, and three others (14%) underwent subsequent procedures, which were not for the infection and did not involve revision of any of the ankle arthro-

plasty components. The authors of this study concluded that TAA may be a viable option for patients with a history of infection of the ankle [3].

While this study does demonstrate the potential for infection-free survival of a TAA in patients with a history of infection in or around the ankle, the follow-up of the cohort is too short to allow conclusive recommendations to be made regarding this patient population. Therefore, further studies on the topic are needed. In the interim, we recommend that all patients with infection in or around an ankle that is being considered for TAA be worked up for infection prior to the elective arthroplasty. During the arthroplasty, additional measures should be implemented to reduce the risk of subsequent SSI/PJI.

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Authors: Jonathan Kaplan, John M. Embil

QUESTION 7: During draping for total ankle arthroplasty (TAA), should the foot be prepped into the surgical field or be covered?

RECOMMENDATION: There is insufficient data demonstrating any advantage or disadvantage to covering the toes during TAA.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Multiple studies have shown increased rates of bacterial colonization in the toes after skin preparation [1–4]. Zacharias et al. reported on the pre-procedural cultures in 12 patients who underwent lower extremity orthopaedic surgery not involving the foot [4]. The authors performed pre-procedural toe cultures, prepared the extremity with povidone-iodine and followed with coverage of the toes with a self-adherent wrap. The authors found a 75% rate of positive pre-procedural and aerobic cultures, concluding that there is some benefit to applying sterile draping to the toes in order to minimize the risk of infection. However, the major weaknesses of the latter study are the small sample size (n = 12), lack of a control group, preparation of the surgical site being done by an operating room nurse not aware of the study and the use of povidone-iodine.

In another study, Brooks et al. demonstrated that there was a significantly lower rate of bacterial recolonization in patients who underwent a standard antiseptic technique in combination with sliding a gauze swab soaked in topical antiseptic multiple times between the toes compared to standard antiseptic technique alone [1].

Hort and DeOrio designed a study that assessed the amount of residual bacterial contamination after surgical preparation of the foot and ankle with or without the use of alcohol [2]. In this study, the 49 patients were randomly assigned to either a standard preparation with chlorhexidine gluconate home scrubs and preoperative povidone-iodine or a standard preoperative preparation with the addition of 70% alcohol. While there was a trend towards significance, the authors found no significant difference in colonization rates with or without the use of alcohol. However, they found high rates of residual colonization (35% in the standard surgical group and 57% in standard preparation plus alcohol). Subsequently, the authors' conclusions included the recommendation of covering the toes during hindfoot and ankle surgery. No patient had any clinical evidence of infection or wound problems. It should be noted, however, that this study did not specifically compare patients with their toes uncovered or covered.

However, despite the presence of studies recommending covering the toes to decrease the risk of contamination in lower extremity surgeries, there are limited studies assessing the rates of infection with the toes covered versus uncovered. Goucher et al. performed a prospective, randomized study to assess the effect of covering the toes during hindfoot and ankle surgery [5]. In this study, they performed three sets of cultures (before skin prep, immediately after skin prep and after the conclusion of the surgery) from the foot and toes from one group of 20 patients with their toes covered and a second group of 20 patients with their toes uncovered. Of 40 patients, only two postoperative cultures were positive, and neither of these patients showed any signs of postoperative infection. Additionally, while seven patients showed signs of superficial infection (erythema, superficial dehiscence or suture abscess), there was no difference between the two groups. Therefore, the authors concluded that there were no benefits in covering the toes in hindfoot and ankle surgery.

Recently, the order of skin preparation has also been investigated. Hunter et al. performed a prospective, randomized control study to assess the proper order of skin preparation of foot and ankle orthopaedic surgeries [6]. The authors found that there were lower rates of positive post-procedural cultures in patients undergoing preparation with isopropyl alcohol followed by chlorhexidine compared to patients undergoing preparation with chlorhexidine followed by isopropyl alcohol. However, no assessment was performed comparing coverage versus non-coverage of the toes during the procedure.

Although inconclusive, there is ample evidence of persistence of bacterial colonization irrespective of skin preparation technique of the foot. Consideration should be given to covering the toes to limit the risk of contamination of the surgical site and the potential for subsequent infection.

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QUESTION 8: Should antibiotic-impregnated cement be used during primary total ankle arthroplasty (TAA)?

RECOMMENDATION: Unknown. There is insufficient evidence for the routine use of antibiotic-impregnated cement during primary TAA.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The main sources for this systematic review were the Medline, Embase, CINAHL and Cochrane CENTRAL databases, beginning with the first citation of ankle arthroplasty in July 2003, the 2016 Swedish Ankle Registry [1] and the 2016 New Zealand Joint Report [2].

In their report on the New Zealand Joint Registry, Rothwell et al. reported on 1,261 TARs from January 2000 to December 2015. Cement fixation was used only in 13 tibial components and in seven talar components. Antibiotic-impregnated cement was used seven times for tibial component fixation and three times for the talus component fixation. However, there was no statistical evaluation in this registry for the item periprosthetic joint infection (PJI) according to the type of cement used.

Considerable research is available related to PJI and antibiotic-impregnated cement for total knee arthroplasty (TKA) procedures. Gutowski et al. stated in their study that the absolute rate of infection increased when antibiotic-loaded cement was used in TKA, although this was less when compared to infection rates after use of plain cement [3]. In 2016, Schiavone et al. performed a systematic review determining the effectiveness of utilizing antimicrobials and the safety of antibiotic-loaded bone cement in primary TKA [4]. The authors concluded that there was no significant difference in the rate of deep or superficial surgical site infection in patients receiving antibiotic-impregnated cement in primary TKA compared with those receiving plain cement.

Based on the lack of proven efficacy for antibiotic-impregnated cement in the prevention of PJI in the TKA literature and the lack of research into antibiotic-impregnated cement in TAA, we cannot provide a recommendation for or against the routine use of antibiotic-impregnated cement during TAA. However, this point may be of limited current importance anyway, as the majority of modern generation TAA are cementless in design.

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1.2. PREVENTION: NON-TOTAL ANKLE ARTHROPLASTY-SPECIFIC

Authors: Gaston Slullitel, Yasuhito Tanaka, Ryan Rogero, Valeria Lopez, Eiichiro Iwata, Yusuke Yamamoto

QUESTION 1: What are the benefits and risks associated with the use of vancomycin powder in the wound during total ankle arthroplasty (TAA) or other foot and ankle procedures?

RECOMMENDATION: Though one study supporting topically-applied vancomycin has shown it to reduce the rate of deep infection in diabetic patients undergoing foot and ankle surgery, there is insufficient evidence to show benefits or to show any risks associated with the use of vancomycin powder during TAA or other foot and ankle procedures in a general population.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The effects of the use of vancomycin powder in foot and ankle surgery are ill-defined. Wukich et al. evaluated the use of vancomycin powder exclusively in foot and ankle procedures, though this was performed in a population composed solely of patients with diabetes mellitus [1]. The authors concluded that odds of surgical site infections (SSIs) (73% decrease) and deep infections (80% decrease) were significantly reduced in diabetic patients who underwent reconstructive surgery of a foot and/or ankle deformity or trauma and received topically-applied vancomycin when compared with a group of patients who did not receive topically-applied vancomycin. The rate of superficial infections did not differ significantly between the two groups. Based on this retrospective controlled study, the authors concluded that foot and ankle surgeons may consider topically applying 500 to 1,000 mg of vancomycin powder prior to skin closure in patients who are not allergic to vancomycin. To our knowledge, no others studies have evaluated the use of vancomycin powder exclusively in foot and ankle surgery.

The effectiveness of vancomycin powder has been documented more extensively in other orthopaedic subspecialties than foot and ankle [2–6]. A systematic literature review by Kanj et al. showed local vancomycin-impregnated cement and powder to be associated with lower infection rates while also being safe and effective in clean orthopaedic surgery [2]. The authors especially recommended utilizing local vancomycin in spine surgery, in which patients without local antibiotic prophylaxis were more than four times more likely to experience a deep postoperative wound infection. Evaniew et al. concluded through their meta-analysis that there is a lack of high-quality evidence to inform the use of intrawound vancomycin in spine surgery [3]. Xie et al. found from their meta-analysis on intrawound vancomycin in spinal surgery that the odds of developing postsurgical wound infection without prophylactic local vancomycin use were 2.83-fold higher than the odds of experiencing wound infection with the use of intrawound vancomycin [4]. Furthermore, a retrospective review performed by Singh et al. that assessed the efficacy of intraoperative vancomycin powder administration on preventing deep SSI in high-energy lower extremity trauma (including tibial plateau fractures and pilon fractures) found that the rate of deep SSI between the groups was not statistically significantly different [7].

Concerns have been raised about the potential risks of the local use of vancomycin, including selection for gram-negative and multi-drug-resistant bacteria, increased local tissue irritation, hypersensitivity or anaphylaxis, impaired renal function, and increased seroma formation [8]. However, these adverse effects are mostly hypothetical and have not been reported in the literature, though a case of circulatory collapse due to topical vancomycin application during spine surgery was identified [9].

Although vancomycin powder appears to be effective at decreasing postoperative infections in spine surgery according to some studies, a large void remains in the evidence for other orthopaedic subspecialties, especially foot and ankle. Randomized controlled trials, particularly within the fields of arthroplasty and trauma, are needed to determine the efficacy of local vancomycin powder for infection reduction. In this scenario, a phase III prospective randomized clinical trial is being conducted among high-risk tibial fracture patients to assess the efficacy of locally administered vancomycin powder in the prevention of SSI after fracture surgery [10], which may bring increased clarity to this matter.

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Authors: Kristin Englund, Nima Heidari

QUESTION 2: Is there a role for the use of dilute povidone-iodine (betadine) irrigation or other antiseptic irrigation solutions during total ankle arthroplasty (TAA) or other foot and ankle procedures?

RECOMMENDATION: With regards to TAA, there is a lack of evidence to recommend for or against the use of betadine solution.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

In 2016, the World Health Organization (WHO) published guidelines for the prevention of surgical site infections (SSIs) [1]. Based upon a review of 17 randomized controlled trials, there is moderate quality evidence that alcohol-based antiseptic solutions for preparation of the surgical site decrease the risk of SSIs in comparison to aqueous solutions. A low quality of evidence showed decreased SSI risk with alcohol-based chlorhexidine gluconate compared to alcohol-based betadine. While alcohol may be concerning for persons from certain religions, the WHO guideline highlights the statement issued in 2002 by the Muslim Scholars Board of the Muslim World League. According to the Board, medicines containing alcohol may be used as an external cleaner. With the use of alcohol-based agents, care must be taken to allow them to dry completely, as operating rooms fires have been reported. According to the Centers for Disease Control and Prevention (CDC), skin preparation with an alcohol-based antiseptic solution should be completed prior to surgery, to reduce the risk of SSI [2].

A systematic review and meta-analysis of combination chlorhexidine gluconate (CHG) and betadine implicated the utility of these agents, despite the low quality of the evidence. A major limitation of many of these studies, however, was the use of bacterial colonization as an endpoint rather than the development of a true SSI [3].

Privitera et al. recently provided a meta-analysis updating and clarifying issues from prior meta-analyses which had not clearly distinguished among studies using alcohol and aqueous-based products. In the updated meta-analysis, there was subgroup analysis showing decreased colonization rates with chlorhexidine, but there was not a statistically significant difference in SSI due to the low numbers of SSI [4].

Although the use of antiseptic agents for skin preparation is necessary for bioburden reduction and prevention of infection, there is minimal data available regarding the role of antiseptic irrigation solutions during TAA. The use of antiseptic agents for irrigation is often performed in the setting of periprosthetic joint infections (PJI) of the hip and the knee, although the utility in total ankle replacements is unknown.

Randomized controlled studies have evaluated the use of various irrigates in open fracture wounds, noting that normal saline was more efficacious and as effective at decreasing infection in comparison to castile soap and bacitracin solution, respectively [5,6]. Chlorhexidine solutions have been evaluated in an in vitro model as being beneficial to decreasing the biofilm load, particularly at concentrations above 2%. However, of importance is that concentrations as low as 0.02% CHG have shown to lead to fibroblast toxicity [7,8]. Dilute betadine may be advantageous in this regard, as it has minimal cellular toxicity at low concentrations and excellent efficacy for prevention of infection [9].

Based on the available data, the CDC has recommended that strong consideration should be given to the use of dilute betadine during all surgical procedures. Although no data in TAA exists, extrapolating the recommendations of the CDC to TAA appears to be reasonable as dilute betadine is inexpensive, efficacious and carries little-to-no cell toxicity.

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Authors: Nima Heidari, Alexander Charalambous, Iris Kwok, Alexandros Vris, Yueyang Li

QUESTION 3: Does revascularization prior to foot and ankle surgery reduce the incidence of surgical site infection (SSI)?

RECOMMENDATION: Several studies support the effect of peripheral vascular disease (PVD) on wound healing and SSI. Despite this, there have been no specific studies proving the beneficial effect of revascularization on SSI prior to surgical intervention in the setting of traumatic or elective foot and ankle surgery. The majority of studies on revascularization are in the setting of diabetic foot infection or established ischemia.

We recommend that in the presence of an inadequate vascularization in the foot and ankle, vascular optimization should be undertaken prior to elective surgery.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Oxygenation of soft tissues is a critical component of wound healing, with wound tissue oxygen tension having a direct correlation with the risk of postoperative wound infection [1].

Diabetes mellitus (DM) and its complications, such as PVD, have proven to be risk factors for increased infection and complication rates after surgery for ankle fractures [2–4]. A large cohort study of

over 57,000 patients found that PVD alone was a strong risk factor for the development of complications after ankle fracture fixation, with the rate of infection increased from 1.44% to 6.87% in the presence of PVD [2].

Diabetes and PVD are associated with increased complications in other forms of foot and ankle surgery, as well [5]. PVD is a proven risk factor for infection after arthrodesis procedures of the foot and ankle and is an independent risk factor for periprosthetic joint infection (PJI) following total ankle arthroplasty [6,7].

Clinical guidelines for the management of diabetic foot disorders suggest a thorough assessment for vascular risk factors prior to surgery [8]. PVD and poor oxygen delivery to tissues are associated with poor wound healing in these patients and should thus be identified [9,10]. Angiography should also be performed when appropriate to assess the potential for revascularization [8], as this intervention has shown to improve the level of amputation and tissue loss in this group of patients [11–13]. Furthermore, Faglia et al. demonstrated revascularization in diabetic patients with critical limb ischemia to lead to a low rate of early amputation [14].

Aust et al. reported that combining revascularization with surgical intervention results in improved wound perfusion and healing of chronic wounds [15]. Revascularization prior to surgery can even allow for successful primary closure of some chronic wounds, according to Barshes et al. [16]. Furthermore, two groups have reported that if primary closure is not viable, then revascularization can be completed in the setting of free tissue for chronic wounds [17,18].

Transmetatarsal amputation can be an effective method of limb salvage in the ischemic or infected diabetic foot, and the rates of wound healing and limb salvage have demonstrated to be improved in conjunction with revascularization [19,20]. Additionally, it is important to understand that the timing of revascularization prior to surgery has not been shown to influence outcomes [21,22]. This would suggest that revascularization prior to diabetic foot surgery is not essential but beneficial when performing revascularization close to foot and ankle surgery in the diabetic patients.

There is little literature related to the effect of revascularization in preventing SSI in foot and ankle surgery. While the presence of PVD is known to increase the risk of SSI/PJI in patients undergoing foot and ankle procedures, no specific study demonstrates revascularization of the foot and ankle obviates this increased risk.

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Authors: Irvin Oh, Kristin Englund

QUESTION 4: Are prophylactic perioperative antibiotics required for isolated forefoot procedures, such as hammertoes?

RECOMMENDATION: Though limited clinical data exists, the administration of perioperative antibiotics is not required for isolated forefoot procedures in the absence of any risk factors, such as immunodeficiency or diabetes mellitus.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 67%, Disagree: 25%, Abstain: 8% (Super Majority, Weak Consensus)

RATIONALE

One high-quality and one moderate-quality prospective randomized control study have demonstrated that there is no significantly different rate of infection in patients who received perioperative antibiotics compared to those who did not receive antibiotics [1,2]. There are also multiple other low-quality studies to support this finding.

A prospective randomized controlled trial of 100 adults undergoing toe fusion with Kirschner wires (K-wires) revealed no significant difference in the infection rate between the group that received prophylactic antibiotics (6.2%) versus the group that did not receive antibiotics (1.9%) [1]. Additionally, a recent multicenter, double-blinded, randomized clinical trial of 500 patients undergoing removal of orthopaedic implants from the lower extremity in the Netherlands showed no significant difference between the group that received a single preoperative dose of intravenous cefazolin (13.2%) when compared to the group that received saline (14.9%) [2].

In their retrospective analysis of 555 patients who underwent elective foot and ankle surgeries, Zgonis et al. reported a 1.9% rate of infection in those who received preoperative antibiotics, compared to a 1.4% rate in patients who did not receive preoperative antibiotics [3]. The authors concluded that prophylactic intravenous antibiotic use in routine elective foot and ankle surgery is not warranted.

Based on a systematic review of the literature, the American College of Foot and Ankle Surgeons has made a recommendation that although there is little to no empiric evidence to support administrating prophylactic antibiotics in elective foot and ankle surgical procedures, antibiotics should be considered [4,5]. They concluded that there is a relative divide between empirical science and common practice. Despite the absence of evidence to support the use of prophylactic antibiotics, it is nevertheless widely used and is a requirement of most hospital systems in order to satisfy quality measures. They justified the practice as being an intervention without significant risk. However, the cost to the healthcare system or the potential for the emergence of resistant organisms was not considered in their 2015 and 2017 statements.

In a survey emailed to all active and candidate members of the American Orthopaedic Foot and Ankle Society, Ruta et al. reported that the majority (75%) of orthopaedic foot and ankle surgeons use prophylactic postoperative oral antibiotics [6]. Most surgeons (69%) prescribed antibiotics to fewer than 25% of patients, although 16% of surgeons prescribed for all elective cases. The finding of the survey was that there was no significant difference in surgical site infection rate among the patients of surgeons who prescribed antibiotics versus those who did not. Another national survey study showed that 25% of attending physicians at foot and ankle fellowships in the United States would administer perioperative antibiotics for foot and surgeries that require K-wire fixation [7].

There is no scientific evidence to support the administration of prophylactic intravenous antibiotics in elective forefoot surgeries. However, even with the lack of high-quality clinical studies, the administration of perioperative antibiotics as a quality measure for most hospital systems and being considered a common practice have led surgeons to administer perioperative antibiotics for forefoot surgeries.

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Diagnosis

2.1. DIAGNOSIS: TOTAL ANKLE ARTHROPLASTY-SPECIFIC

Authors: Michael Aynardi, Milena M. Plöger, K.C. Walley, C.B. Arena

QUESTION 1: What is the definition of acute and chronic periprosthetic joint infection (PJI) of total ankle arthroplasty (TAA)?

RECOMMENDATION: There is a paucity of data for defining acute or chronic PJI following TAA in the literature. Any discussion of PJI after ankle replacement is entirely reliant on the literature surrounding knee and hip arthroplasty.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE:

PJI after TAA is an unfortunate and serious complication that bears significant consequences to the patient and impediments to the natural history of ankle replacement, often prompting revision arthroplasty, conversion to arthrodesis or potentially below-the-knee amputation. While the practice of TAA has gained popularity in recent years [1], there is a paucity of data describing wound complications and acute or chronic PJI of TAA. The review of the current literature fails to identify a specific set of accepted criteria for defining an acute or chronic PJI of TAA.

Diagnostic criteria of acute or chronic PJI (non-specific to TAA) is guided by the definition developed by the Musculoskeletal Infection Society, which was later modified in 2013 by the International Consensus Group on Periprosthetic Joint Infection (Table 1) [2]. Diagnosis of PJI requires the presence of one major criterion or presence of at least three of five minor criteria. Acute infections were defined by presentation within 90 days of index surgery and chronic infections after 90 days. Acute and chronic infections each have a different set of threshold levels for the minor criteria (Table 1) [2].

The current literature regarding ankle replacement is significantly limited in data available on PJI. Of the studies that reference diagnosis of PJI in TAA, only one study by Alrashidi et al. offers any explicit reference to a diagnostic algorithm used to classify patients with periprosthetic ankle infections [1]. While not explicitly delineated, the authors appear to invoke laboratory threshold measurements described by the International Consensus Group on Periprosthetic Joint Infection in their proposed diagnostic diagram. Our systematic review failed to identify any clinical study or publication that had implemented or referenced the diagnostic algorithm submitted by Alrashidi et al.

While Alrashidi et al. have presented the most comprehensive and systematic pathway to date specific to diagnosing a PJI in TAA [1], the criterion utilized in this pathway are derived from previously described literature specific to knee and hip arthroplasty [2,3]. TAA data is significantly more limited and thus difficult to establish statistically significant infectious indicators specific to the ankle joint. Alrashidi et al. present clinically useful data in their diagnostic algorithm including the presence of a sinus tract, cell count, and differential from synovial aspiration, culture from synovial aspiration, nuclear imaging studies and histological frozen sections. However, no sensitivities or specificities of the results have been described in determining PJI specific to TAA. Ferrao et al. also described similar work-up in diagnosing PJI in TAA including clinical history, physical examination, radiographic evaluation and laboratory values [4]. Pertinent history, such as sudden onset of pain, swelling, drainage, fever and associated clinical findings, such as tenderness, increased local temperature and effusion, were components concerning for PJI as described by the authors. This study presented a similar diagnostic pathway, including inflammatory markers and joint aspiration, and also made reference to the hip and knee arthroplasty literature in setting criteria and thresholds [5–7]. The trend of referencing hip and knee arthroplasty data in the work-up of PJI in TAA in our systematic review was common in the literature [8–14].

Patton et al. define PJI by positive preoperative or intraoperative cultures or the presence of chronic draining sinus tract, but do not provide reference for this definition [15]. Meyerson et al. similarly defined PJI by draining sinus tract, positive preoperative aspiration (purulent aspirate, positive Gram stain and/or elevated leukocyte count > 1,000 per mm^3) or positive intraoperative culture [16]. The authors subdivided infections into acute and chronic, but did not specify criteria for differentiating between the two. Kessler et al. defined PJI as clinical signs of infection plus at least one of the following: (1) same bacteria grown on two separate preoperative or intraoperative cultures, (2) visible pus surrounding the joint, (3) acute inflammation on histopathological examination (> 10 neutrophils/HPF) or the ability to probe the base of the wound to the implant) [10,11].

Other mentions of PJI in TAA in our literature search did not specifically describe the criteria used to reach that diagnosis [9,17–19]. Case reports of PJI in TAA were also described without defining parameters for diagnosis of acute or chronic infection [20,21]. Further review did demonstrate several manuscripts, which identified risk factors for PJI, including proximity to dental procedures or medical comorbidities but failed to provide a definition for diagnosis of acute or chronic PJI [22,23]. Our systematic review yielded definitions of acute and chronic PJI defined in total hip and knee literature, case

TABLE 1. Diagnostic criteria of periprosthetic joint infection according to the International Consensus Group on Periprosthetic Joint Infection

Major Criteria		
• Identification of 2 positive periprosthetic cultures with phenotypically identical microorganisms OR • Presence of a sinus tract communicating with the joint		
Minor Criteria		
• Elevated serum CRP AND elevated ESR • Elevated synovial fluid WBC count OR ++ change on leukocyte esterase test strip • Elevated synovial fluid PMN% • Positive histologic analysis of periprosthetic tissue • A single positive culture		
Threshold Levels for minor criteria for PJI		
Criterion	**Acute PJI**	**Chronic PJI**
ESR (mm/h)	Not helpful with no defined threshold	30
CRP (mg/L)	100	10
Synovial WBC count (cells/ µl)	10,000	3000
Synovial PMN %	90	80
Leukocyte esterase	+ OR ++	+ OR ++
Histologic analysis of tissue	> 5 neutrophils per HPF (x 400) in 5 HPF	

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PMN%, polymorphonuclear neutrophil percentage; WBC, white blood cell count; HPF, high-powered field; PJI, periprosthetic joint infection, mm/h, millimeters per hour; µl, microliters. (Adapted with permission [2].)

reports, as well as suspected risk factors, signs, symptoms and history related to PJI.

In summary, there remains no definitive criterion in the literature for defining acute or chronic PJI after ankle arthroplasty. In the absence of specific diagnostic criteria for PJI of TAA, we may need to rely on the literature related to total hip arthroplasty and total knee arthroplasty to investigate this area further. A recent study published offers an evidence-based and validated definition for PJI of the hip and knee [24]. The criteria based on pretest probability offer each diagnostic criteria a score that is commensurate with the performance of the test in the pre-test probability and diagnostic odds ratio [24].

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QUESTION 2: What is the diagnostic "algorithm" for infected total ankle arthroplasty (TAA)?

RECOMMENDATION: Patients who present with clinical symptoms and signs of periprosthetic ankle infection (pain, erythema, warmth, sinus tract, abscess around the wound) and sinus tracts communicating with the ankle/subtalar joint are likely to have TAA infection.

In the absence of a sinus tract, elevated inflammatory markers (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)) should prompt ankle joint aspiration for cell count, differential and culture. The joint aspiration is to be repeated.

If the same organism is identified in at least two cultures of synovial fluid, the patient is diagnosed to have an infection. If the repeat aspiration is negative, further investigation is warranted.

In patients not requiring surgical intervention for other reasons, nuclear imaging should be considered for diagnosis. If an operation is indicated, histologic examination (> 5 neutrophils/high-power field) or synovial fluid analysis is conducted to confirm infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Diagnosis of infected TAA is mainly guided by the periprosthetic joint infection (PJI) diagnostic criteria developed from the MusculoSkeletal Infection Society (MSIS) and the International Consensus Meeting [1–3]. Although the current PJI diagnostic criteria were developed based on hip and knee patients, the majority of the infected TAA clinical studies have employed the same or a variation of the MSIS criteria [3–9]. The major diagnostic criteria include (1) presence of a sinus tract which communicates with the joint or (2) two positive cultures isolating the same pathogen from the periprosthetic tissue or synovial fluid samples [1–3]. Minor criteria include elevation of inflammatory markers (CRP, ESR), elevated synovial fluid white blood cell (WBC) count or change on leukocyte esterase test strip, elevated synovial fluid polymorphonuclear cells, positive histologic analysis of periprosthetic tissue and single positive culture [1–3]. The above diagnostic algorithm was also recommended by the same authors [1–3].

Systematic literature reviews and meta-analyses have shown a 0 to 4.6% occurrence of deep infection after TAA [10,11]. Myerson et al. reported a 3.1% infection rate after TAA [6]. Their criteria for diagnosis was based on clinical findings of swelling, inflammation, drainage or persistent wound problem which prompted the protocol of joint aspiration for culture and microscopy. Synovial fluid analysis and lab analysis of inflammatory markers (CRP, ESR, WBC count) were tested to confirm infection. Patton et al. utilized similar criteria and reported a 3.2% rate of ankle PJI [7]. Usuelli et al. employed the same diagnostic criteria suggested by the MSIS and reported a 3.7% deep infection rate in the anterior approach group compared to a 1.4% deep infection rate in lateral approach group [9].

However, some authors have raised the possibility that the current MSIS guideline for diagnosis and treatment of hip and knee PJI may be different from the ankle joint, given the relatively thinner soft tissue envelope and limited number of patients who underwent successful joint-preserving revision ankle arthroplasty [3,5]. Moreover, no clinical study has validated utilization of the current hip and knee PJI diagnostic criteria for ankle PJI. Therefore, a high-quality clinical investigation is needed to validate the current criteria and algorithm for diagnosis and treatment of the ankle PJI.

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QUESTION 3: What tests are useful to investigate a possible infection of total ankle arthroplasty (TAA)? What are their thresholds?

RECOMMENDATION: Overall, the approach to a potentially infected TAA does not change compared to other periprosthetic joint infections (PJIs). There are no novel or unique diagnostic procedures for TAA infection, specifically. Joint aspiration or intraoperative tissue/synovial biopsies with microbiological cultures are the most important diagnostic tests for suspected TAA infections. In the absence of specific data related to TAA, the threshold for these tests should be derived from the hip and knee PJI literature.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The literature lacks information regarding a specific diagnostic work-up for infected TAA compared to PJI of other joints. Clinically, persistent pain with or without loosening of the components is believed to be a potential presentation for PJI of TAA [1–3]. According to some authors, the pain localization can hint at one diagnosis versus another; anteromedial pain is commonly caused by gutter impingement or medial ankle stress reaction, whereas more diffuse pain is usually associated with stiffness, loosening or infection [3]. A prior history of delayed surgical wound healing is often reported in patients with infection [4]. The presence of a sinus tract is definitive evidence of infection but is infrequently seen [4].

Ankle swelling and pain progressing to incisional discharge then dehiscence and rapid loosening are strongly suggestive of infection. In these cases, a joint aspiration or intraoperative tissue/synovial biopsies and microbiological work-up, remains the preferred method for diagnosis of TAA infections [2–7]. The microbiological techniques (culture, polymerase chain reaction) are not specific for TAA infections. In infected TAA literature that identifies the causative pathogen, there is a trend towards TAA PJI being affected by a higher proportion of gram-positive microorganisms compared to other PJIs and a smaller proportion of gram-negative bacteria [4,5]. Of note, the microbiological evaluation in one study found no single gram-negative bacteria among 19 cases of infected TAA [7]. Intra-articular leukocyte differentiation, leukocyte esterase, intra-articular C-reactive protein, or alpha-defensin immunoassays of prosthetic joint samples have not yet been sufficiently validated for TAA PJI [8]. Other than during the initial work-up to rule out infection, systemic serum inflammatory markers are practically of no additional advantage. Many authors do not dogmatically recommend their use [3]. Likewise, imaging techniques do not prove infection but may show the localization of abscesses or may confirm implant loosening [1]. Hsu et al. suggested that more than 10 leukocytes per high-power microscopic field in the synovial biopsies would be suggestive of infection [1]. Other groups have reported that >5 leukocytes per high power field in frozen section microscopy may be indicative of PJI [5,7]. However, these approaches are not shared with the majority of author groups and convincing data in favor of microscopic leukocyte counting for TAA specifically are lacking.

Ultimately, there is little consensus regarding the work-up for TAA PJI. Many diagnostic tools are used based on provider preference, with only aspiration and fluid analyses being universally endorsed in the literature.

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QUESTION 4: What are the indications for aspiration of a possibly infected total ankle arthroplasty (TAA)?

RECOMMENDATION: Whenever a periprosthetic joint infection (PJI) of a TAA is clinically possible or suspected, especially when elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels exist, and in correspondence to the literature on PJI in total hip and knee arthroplasties, joint aspiration is indicated.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

We performed a systematic review of the literature regarding the research question found above as recommended: A PubMed Search for the MeSH Terms ("arthrocentesis"[MeSH Terms] OR "arthrocentesis"[All Fields] OR ("joint"[All Fields] AND "aspiration"[All Fields]) OR "joint aspiration"[All Fields]) AND ("arthroplasty, replacement, ankle"[MeSH Terms] OR ("arthroplasty"[All Fields] AND "replacement"[All Fields] AND "ankle"[All Fields]) OR "ankle replacement arthroplasty"[All Fields] OR ("total"[All Fields] AND "ankle"[All Fields] AND "arthroplasty"[All Fields]) OR "total ankle arthroplasty"[All Fields]) was performed on February 16, 2018. A total of n = 10 results were found.

Additionally a PubMed Search for the MeSH Terms ("infection"[MeSH Terms] OR "infection"[All Fields]) AND ("arthroplasty, replacement, ankle"[MeSH Terms] OR ("arthroplasty"[All Fields] AND "replacement"[All Fields] AND "ankle"[All Fields]) OR "ankle replacement arthroplasty"[All Fields] OR ("total"[All Fields] AND "ankle"[All Fields] AND "arthroplasty"[All Fields]) OR "total ankle arthroplasty"[All Fields]) was performed on February 17th, 2018. A total of n = 200 results were found. After exclusion of irrelevant manuscripts or duplicates, only four publications remained that can be considered a "match" regarding a specific answer to the research question.

Investigation of a prosthetic joint for possible infection, including the ankle, commences with detailed history-taking, physical examination and ordering a series of laboratory tests. There is no gold standard for diagnosis of PJI and because of this, we must rely on a combination of diagnostic techniques to reach or refute the diagnosis of PJI. The serum laboratory tests that should be ordered include ESR, CRP and potentially other tests, such as D-dimer levels. If these laboratory tests are elevated or with normal serological tests and high clinical suspicion for infection, the next line of investigation is believed to be joint aspiration.

The synovial fluid obtained, if any, should be sent for analyses that include total white blood cell count, neutrophil count and the percentage of neutrophils, as well as analyses for biomarkers, such as leukocyte esterase and alpha-defensin. The joint aspirate is also cultured to identify the potential infecting pathogen.

Although the algorithm for investigation of PJI in hip and knee arthroplasty has been well studied and the optimal threshold for parameters, such as cell count and neutrophil differential, determined, there is little data related to PJI of TAA. In the absence of such data, we believe that TAA should also be investigated in a similar fashion to hip and knee arthroplasty. In fact, our search determined that most studies related to TAA use the MusculoSkeletal Infection Society criteria and extrapolate data published in total hip and knee arthroplasty literature to TAA [1]. In one study, Alrashidi et al. recommended that aspiration for synovial fluid analysis should be considered if the ESR and CRP are elevated [2]. This has been corroborated by other studies in recent years, confirming the utility of aspiration to help gauge the presence of inflammation or infection around a TAA [3–5].

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QUESTION 5: What is the best technique for performing aspiration of patients with total ankle arthroplasty (TAA)?

RECOMMENDATION: In the absence of evidence, we recommend that ankle joint aspiration to evaluate for periprosthetic joint infection (PJI) be performed under sterile conditions via the anteromedial approach. Ultrasound guidance may be used if available but is not necessary to obtain an acceptable synovial fluid sample.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

In the setting of suspected ankle PJI based on preoperative history, physical, laboratory values and imaging modalities, preoperative aspiration can be useful and may reveal an organism in 50 to 60% of cases [1]. Landmark-based aspiration using a sterile technique via an anteromedial approach performed in the office is most commonly performed in order to obtain ankle synovial fluid for analysis. Imaging guidance via computed tomography or ultrasound is not usually necessary since the ankle joint is relatively simple to aspirate [2]. Ultrasound guidance may provide higher accuracy if available based on cadaver studies evaluating injections, which suggested 85% accuracy without ultrasound and 100% accuracy with ultrasound [3,4]. However, another study demonstrated 100% accuracy in ankle joint needle insertion in a cadaver study using palpation technique only [5]. In the setting of infection, there is typically excess fluid resulting in simpler access to the ankle joint for aspiration. Thus, aspiration can be performed without necessarily using ultrasound guidance.

The ankle can be accessed via several approaches. The most common approach is the anteromedial approach, which is just medial to the tibialis anterior tendon at the level of the ankle joint.

No difference was seen between anteromedial or anterolateral approaches in a cadaver study when performed by orthopaedic trainees, and there was an 80% success rate of being intra-articular with both approaches [6].

The risk of bacterial contamination of the joint after aspiration has not been studied. There is some literature discussing septic arthritis after corticosteroid injection. One report indicated an incidence of 0.5% in a population of patients with rheumatoid arthritis on immunosuppressant medication [7]. In the general population, infection after cortisone injection is reported to range between 1 in 3,000 to 1 in 16,000 [8,9]. It is generally thought to be very rare when a basic sterile technique is used.

We recommend that the site of ankle aspiration is wiped with alcohol and then prepared with the use of another antiseptic agent, such as povidone-iodine or chlorhexidine. Although not absolutely necessary, the site of aspiration may be isolated with the use of sterile towels. The aspiration may be performed in the office setting or the operating room suite, depending on the infrastructure in each facility.

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QUESTION 6: Should aspiration of the ankle with an antibiotic spacer be performed prior to reimplantation?

RECOMMENDATION: We recommend that aspiration of the ankle with an antibiotic spacer prior to a second-stage reimplantation should be strongly considered. Available studies indicate that a positive culture of the aspirate in this setting is predictive of residual infection, while a negative aspirate culture does not rule out infection and should be interpreted in light of other clinical indicators and laboratory values.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 92%, Disagree: 8%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

There have been no studies in the total ankle arthroplasty (TAA) literature that have evaluated the utility of aspiration of an antibiotic spacer as part of a two-stage revision for infected total ankle arthroplasty. In a review article, Alrashidi et al. stated that reimplantation should only be undertaken once the infection is eradicated as indicated by clinical history and examination, serological testing and synovial fluid aspiration [1]. However, no references or evidence is cited to support this assertion. Two large series on the treatment of infected TAA each included two-stage revision with use of an antibiotic spacer as a treatment strategy [2,3]. However, neither study included preoperative aspiration of the antibiotic spacer in the methodology. Of note, Myerson et al. did routinely perform intraoperative examination of tissue and fluid by microscopy during definitive reconstruction surgery in order to evaluate for the presence of polymorphonuclear (PMN) leukocyte count > 5 per high power field or the presence of organisms on Gram stain [2]. If either criterion was met, repeat debridement with antibiotic cement spacer exchange was performed and the definitive reconstruction was deferred.

There have been numerous studies in the total hip and knee replacement literature investigating the utility of aspiration of antibiotic spacers. While these have provided valuable data, it should be noted that these studies were largely retrospective and non-uniform. The definition of the presence of infection was also not clear in some of these studies, and positive culture was considered by many studies as the gold standard. Some studies also correlated the results of the aspiration and intraoperative findings with the ultimate success or failure following reimplantation. The studies also have significant variability in the duration of antibiotic treatment as well as variability in the presence/absence and duration of an antibiotic holiday.

Studies regarding aspirate cultures of antibiotic spacers for infected total knee arthroplasty reported generally better specificity than sensitivity. Specificity ranged from 61 to 100% while sensitivity ranged from 0 to 83% [4–8]. Positive predictive value ranged from 0 to 100% while negative predictive value ranged from 74 to 97% [4–8]. Aside from cultures, additional aspiration tests have been evaluated for accuracy. There is significant variability across reported cut-off values and sensitivity and specificity rates for white blood cell count and PMN% of preoperative aspirates [9–12].

One argument for routine aspiration of an antibiotic spacer of the hip or knee prior to reimplantation revolves around the relatively low cost, simplicity and low risk of the procedure. However, in the setting of a temporary antibiotic spacer of the ankle, there is no evidence regarding the success rate of attempted aspirations.

One challenge that exists is the interpretation of a dry aspiration. In the hip, consideration has been given to performing a saline

lavage in order to improve the yield of aspiration. Newman et al. reported that saline lavage predictably affected the results of synovial cell counts and their diagnostic utility but has a less substantial effect on culture results [11].

In the absence of concrete evidence, with reliance on the available data from the hip and knee literature and taking into account the simplicity of aspirating an ankle joint, we recommend that aspiration of the ankle with an antibiotic spacer be strongly considered prior to reimplantation. The analysis of the aspirate fluid, if obtained, will provide valuable data that can influence the intended procedure and the ultimate success and failure of reconstruction.

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QUESTION 7: Is there a role for measuring synovial biomarkers for diagnosis of infected total ankle arthroplasty (TAA)?

RECOMMENDATION: Based on the hip and knee arthroplasty literature, measuring synovial biomarkers may play a role in the diagnosis of infected TAA. The diagnosis of periprosthetic joint infection (PJI) in the setting of a TAA can be confirmed with cultures, provided that a plausible pathogen is recovered in the context of a compatible clinical picture. In the absence of a positive culture, synovial biomarker analysis may help in establishing the diagnosis.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 8%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

TAA has emerged as a successful procedure, improving both pain and function in patients with end-stage arthritis of the ankle, with reported rates of infection ranging from 0 to 4.6% [1]. A specific approach does not yet exist for the diagnosis of PJI in TAA. However, the traditional approach for the diagnosis of PJI in other joints involves joint aspiration and sampling of the synovial fluid for analysis involving synovial white blood cell (WBC) count and differential fluid culture, as well as serum WBC count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels [2,3].

Elevation of several synovial biomarkers has been identified as indicators of potential PJI, including WBC count, percentage of polymorphonuclear cells (PMN%), α-defensin, leukocyte esterase (LE), interleukin IL-1a, IL-1, IL-6, IL-8, IL-10, IL-17, granulocyte colony-stimulating factor (G-CSF), vascular endothelial growth factor (VEGF), CRP, neutrophil elastase 2 (ELA-2), lactoferrin, neutrophil gelatinase-associated lipocalin (NGAL), resistin, thrombospondin and bactericidal/permeability-increasing protein (BPI) [4–6].

Among the previously-mentioned synovial biomarkers, α-defensin is regarded as the most accurate single test for the diagnosis of PJI, with a sensitivity of 97% and a specificity of 96% [5]. Therefore, the accuracy of α-defensin is closest to the 2013 International Consensus Meeting (ICM) criteria for the diagnosis of PJI [6]. Alpha-defensin also appears to provide the most consistent results, regardless of the causative microorganism or its virulence. Its accuracy even remains unaffected in the setting of antibiotic administration to the patient prior to obtaining the synovial fluid sample [4,5,7]. IL-8 has been shown to follow α-defensin in terms of performance, while the accuracy of synovial fluid culture has been shown to have a sensitivity of 62% and specificity of 94% [5]. Synovial fluid leukocyte count (sensitivity of 89% and specificity of 86%) and PMN percentage (sensitivity of 89% and specificity of 86%) both demonstrate accuracy in diagnosing PJI [5,6]. However, they are already part of the six minor criteria for the diagnosis of PJI according to the ICM 2013 definition of PJI [6]. There is great controversy regarding the cutoff point used for the synovial leukocyte count and PMN percentage, which prevents their use as stand-alone diagnostic tests [4,5,8–12].

LE, with a sensitivity of 77% and specificity of 95%, has the advantage of being inexpensive [5,13–16]. However, there is a level of subjectivity present with the interpretation of LE results, in addition to the possibility of the presence of blood in the fluid affecting the results.

The combination of two or more markers to detect PJI has been studied. It has been shown that the combination of synovial fluid α-defensin and CRP provided a sensitivity of 97% and a specificity of 100% in diagnosing PJI [17]. The combined use of synovial CRP and adenosine deaminase (ADA) improves the positive predictive value [18]. A synovial fluid CRP should be included in the synovial fluid analysis and correlated with other lab markers [17].

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QUESTION 8: What is the role of molecular techniques for detection of pathogen deoxyribonucleic acid (DNA) (polymerase chain reaction (PCR) or next-generation sequencing) in patients with infected total ankle arthroplasty (TAA)?

RECOMMENDATION: Molecular techniques, particularly next-generation sequencing and the Ibis T5000 technology, have the potential to be used as an important adjunct in the diagnosis of bacterial infection following TAA, although sufficient clinical evidence is lacking.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The culture of multiple periprosthetic tissue samples is currently considered the gold standard for microbiological diagnosis of periprosthetic joint infections (PJIs) [1]. However, biofilm-associated infections are not easily detected by culture-based methods and are often resistant to conventional antimicrobial therapy. Therefore, it seems imperative to promptly investigate and subsequently integrate molecular diagnostic techniques into the clinical practice for the management of PJI [2].

The most common molecular techniques that have been used to diagnose PJI are both based on PCR: specific PCR and broad-range PCR [3]. Specific PCR targets a single bacterial species (e.g., *Staphylococcus aureus*) or a group of closely-related species (e.g., all staphylococcal species). These are typically considered real-time PCR assays. Specific PCRs can be used in the diagnosis of any targeted pathogen with extreme sensitivity, potentially detecting even a single copy of the target DNA. This approach provides accurate results within hours and has the advantage of singling out any organisms deemed as significant, thereby making contamination easier to control for, as well as making quantification possible [3].

Broad-range PCR, in contrast to specific PCR assays, provides the opportunity to detect DNA from any pathogen rather than a specific preset of expected pathogens. Almost all broad-range PCR techniques utilized in diagnostic microbiology laboratories are based on the gene coding for the small subunit of the bacterial ribosome (16S rDNA). The main limitations of broad-range PCR relate to inherent problems with contamination and sensitivity. Contamination arises from bacterial DNA present in PCR reagents or inadvertently introduced during the collection and handling of the sample, particularly if additional fluids are added to the culture sample during transport or laboratory processing [4]. Unfortunately, these "contaminant" bacteria detected with broad-range PCR are closely related to the microorganisms that cause low-grade

PJI, making the distinction between true-positive versus false-positive PCR results challenging. For these reasons, broad-range PCR has not yet been integrated into the standard routine diagnostic procedure of PJI by most laboratories, but this technique is a valid option to be applied to the diagnosis of synovial fluid or periprosthetic tissue infections [5,6].

Comparing the specific and broad techniques, one study found the sensitivities of specific PCR for detection of *Propionibacterium acnes* and *staphylococcus spp*. in sonication fluid from prosthetic shoulder infections to be 89% and 97%, respectively [7]. In contrast, broad-range PCR of tissue cultures in patients with PJI has previously demonstrated a sensitivity of only 50% [8].

The arrival of high-throughput (next-generation) sequencing techniques has enabled the generation of thousands of individual sequences from a single broad-range PCR [3]. This approach seems to be promising in aiding in surgical site infection and PJI detection, since it provides detailed information on the bacterial population present in prosthetic joint samples [3]. The next-generation technique of pyrosequencing allows for massively parallel, rapid identification of pathogens at a much lower cost per base than the traditional sequencing. The greater breadth and depth of pyrosequencing, in which hundreds of thousands of sequences can be generated in a single run, means that low abundance species have a higher chance of being detected [3].

When comparing molecular and microbiological techniques on PJIs, culture and PCR have shown similar sensitivities (72.6% and 70.4%) and specificities (98.3% and 97.8%) [9,10]. While using a combination of 16S rDNA PCR and lateral flow immunoassay, the 16S recombinant DNA (rDNA) test system provided a diagnostic result within 25 minutes in 97% of all patients. This can be juxtaposed to the microbiological culture of synovial fluid, which achieved a lower sensitivity than that of the 16S rDNA test with 80% [11]. In terms of cost, molecular diagnosis may be a more expensive diagnostic method than bacterial culture with a cost-effectiveness that has not yet been evaluated [12]. The direct detection of bacterial 16S rDNA shows encouraging results and warrants further evaluation in larger patient cohorts [11].

While molecular techniques have shown to be important in diagnosing PJI in orthopaedic fields other than foot and ankle, they have not been well-studied in the setting of an infected TAA. In one of the few studies identified studying the utilization of molecular techniques in the foot and ankle, Stoodley et al. evaluated several techniques to ascertain the presence of a bacterial infection in an explanted TAA that had an initial negative culture. The techniques included the Ibis T5000, real time-polymerase chain reaction (RT-PCR), a direct culture of the ankle hardware, confocal microscopy, and fluorescent in situ hybridization (FISH) [13].

The Ibis T5000, a research use only (RUO) technology based on the combination of PCR amplification of highly conserved pathogen genomes with high-performance electrospray ionization mass spectrometry and base-composition analysis, is able to tease out a variety of organisms (including bacterial and viral) down to the species level [14]. Data points include number of genome copies, relative organism abundance and antibiotic sensitivity [15,16]. Based on Ibis testing, Stoodley et al. were able to identify the presence of *S. aureus*, *S. epidermidis* and the methicillin-resistant *mecA* gene in tissue on the removed TAA hardware [13]. Additionally, the Ibis detected that there was close to ten times more *S. aureus* in comparison to the *S. epidermidis*. Of all the techniques investigated, the authors proposed the Ibis T5000 technology to have the most potential in aiding with clinical detection of PJI with TAA [13].

In addition to the Ibis system, the authors used RT-PCR in order to detect metabolically active *S. aureus* [13]. The authors were able to harvest ribonucleic acid (RNA) from a tissue sample and after converting the RNA to complementary DNA via reverse transcription, they utilized specific PCR primers for the bacterial glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and histidine ammonia-lyase (*hutH*) genes [17–19]. The study demonstrated the presence of *S. aureus* messenger RNA for both the GAPDH and the *hutH* genes [13].

Another technique was a direct culture of the tibial metal component of the removed ankle hardware. After a detailed agar preparation protocol, the tibial component was placed in a beaker in which an agar formed. After incubation, the number of bacterial colony-forming units (CFUs) on the agar was eventually estimated. The authors reported approximately 1000 CFUs spread across the entire tibial component and composed of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *S. epidermis* [13].

Confocal microscopy was also implemented for viability determination after staining and using a 488nm excitation wavelength to identify bacteria as living or dead. Fluorescent in situ hybridization (FISH) was also utilized using fluorophore-labeled 16S rDNA sequences specific for *S. aureus* [20–22]. A red Syto59 fluorescent nucleic acid stain was used to stain all bacterial and host nuclei, allowing *S. aureus* to be the only species stained both red and green. Bacteria that were stained with Syto59 solely were distinguished from host nuclei on the basis of size [22,23]. Confocal microscopy and FISH demonstrated a scattered distribution of biofilm formation, with clusters of bacterial colonies on tissue, the talar component edges, the polyethylene bearing surface and the tibial component. FISH testing also indicated that bacterial growth was predominantly *S. aureus* and *S. epidermidis* to a lesser extent [13].

These findings presented by Stoodley et al. offer to be an important diagnostic step to gauge the presence of a bacterial infected TAA [13]. However, further research is necessary to decide the true clinical utility of these techniques.

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QUESTION 9: Should culture samples be taken during all revision total ankle arthroplasty (TAA)?

RECOMMENDATION: We recommend that intraoperative cultures be taken during revision TAA. The result of intraoperative cultures should be interpreted together with clinical suspicion for infection and the results of the laboratory and imaging investigations. We also recommend that multiple tissue specimens be collected. Given a lack of evidence for routine intraoperative cultures for revision TAA literature, this recommendation is based on analogous evidence in the total hip and knee replacement literature.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

There have been no studies in the TAA literature that have evaluated the utility of routine intraoperative cultures for all revision TAA cases. Multiple case series and review articles on revision TAA have been published which do not specifically advocate for or against this practice [1–4]. Jonck et al. do, however, recommend curettage of any encountered cysts at the time of revision and advise that cyst material should be sent for cell count, microbial culture and histopathology [3]. However, no data is included regarding previous results and utility of these samples.

There have been multiple studies in the total hip and knee replacement literature investigating the role of routine cultures taken during revision arthroplasty for presumed aseptic failure. Barrack et al. published on a series of revision total knee replacements with unexpected positive intraoperative cultures [5]. There were 41 cases with positive cultures out of 692 total cases. Twenty-nine of these cases had only one positive culture without additional evidence of infection and were considered false positives. None of the presumed false positives had long-term signs of infection or required additional surgery. The other 12 cases had multiple positive cultures or one positive culture and an abnormal preoperative inflammatory marker or synovial aspirate. These cases were treated with a four to six week course of antibiotics and two of these patients presented with early recurrent infection requiring a two-stage exchange. An additional patient had aseptic loosening requiring revision at six years, at which time there was no sign of infection and negative intraoperative cultures. The authors recommended routinely sending at least five sets of cultures in the setting of abnormal preoperative inflammatory markers, abnormal synovial aspirate or tissue appearing concerning for infection intraoperatively at the time of revision.

Jacobs et al. reported on 679 cases of revision hip or knee arthroplasty for presumed aseptic failure [6]. Infection was defined by the presence of two or more positive intraoperative cultures with the same organism. The incidence of unsuspected infection was 10%. For total knee replacements, patients diagnosed with infection went on to require repeat revision for recurrent infection at a higher rate compared with patients who were not diagnosed with infection at initial revision. For total hip replacements, there was no significant increased rate of recurrent infection requiring revision. The authors emphasized the importance of improved preoperative work-up prior to revision total joint arthroplasty to minimize the number of unsuspected prosthetic joint infections.

Given that there is a small but significant incidence of unsuspected joint infection in hip and knee arthroplasty, there is likely a similar incidence of unsuspected TAA infection amongst presumed aseptic failures. Routine cultures at the time of revision for aseptic failure may help to identify unsuspected infections. However, even the literature for hip and knee replacement does not provide significant evidence to suggest how to intervene once the diagnosis is made and whether long-term outcomes can be improved once intraoperative cultures lead to the diagnosis of periprosthetic joint infection (PJI).

Therefore, we recommend that all patients undergoing revision ankle arthroplasty be investigated for PJI, which includes measuring serum markers, aspiration of the joint, intraoperative evaluation (which may include histology) and any other necessary tests. The

result of intraoperative culture during revision ankle arthroplasty can then be interpreted in light of laboratory and imaging investigations and any clinical suspicion for infection.

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2.2. DIAGNOSIS: NON-TOTAL ANKLE ARTHROPLASTY-SPECIFIC

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QUESTION 1: What is the optimal number of samples for culture in patients undergoing surgery for foot and ankle infections?

RECOMMENDATION: The optimal number of samples for culture in patients undergoing surgery for foot and ankle infections is unknown. We recommend that multiple tissue samples be taken.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Our search of the literature did not reveal any data regarding the optimal number of culture samples that should be taken during foot and ankle surgery. However, there is high-level evidence in the periprosthetic joint infection (PJI) literature regarding this topic. Bémer et al. conducted a prospective multicenter study evaluating the minimum number of samples required to make an accurate diagnosis of PJI [1]. They determined that four samples were sufficient for diagnosing PJI with the highest mean percentage of agreement (98.1% and 99.7%, respectively) in regards to the bacteriological criterion and diagnosis of confirmed PJI.

Atkins et al. performed a prospective study assessing the effect of sample number on the ability to diagnosis PJI [2]. Their study recommended sending five to six specimens and defined a cutoff of three or more positive operative cultures yielding an indistinguishable organism for definite diagnosis. This recommendation achieves an extremely high specificity, but an impractical sensitivity (it would require too many samples). In order to achieve both excellent sensitivity and specificity, five to six specimens with two or more culture-positive samples are recommended to diagnose infection.

The Infectious Diseases Society of America guidelines [3] provide moderate evidence from more than one well-designed clinical trial, without randomization (B-II evidence) recommending at least three (and optimally five or six) intraoperative tissue samples be submitted for aerobic and anaerobic culture to diagnose a PJI.

The majority of studies related to this subject in regards to the foot and ankle relate to the management of patients with diabetic foot ulcer and osteomyelitis. The available studies have revealed that the yield of culture is dependent on how these culture samples are taken (e.g., swab, bone biopsy and so on) and did not evaluate the influence of the number of culture samples taken.

In 144 diabetic foot ulcer patients with suspected osteomyelitis, ulcer swab and bone biopsy specimens were taken. The authors found that there is poor reliability of the ulcer swab culture in identifying the pathogens causing osteomyelitis in this patient population. When used in conjunction with bone biopsy specimen culture, there may be a more reliable isolate for effective management [4]. Another study reported that swab cultures may have utility for guiding the antibiotic selection for management of low-grade infection. In the setting of higher grade infections, deeper tissue culture and biopsy are necessary [5].

Although there is limited literature guiding the number of samples necessary to obtain for foot and ankle infections, this indicates the need for research in this area. Given the extent of studies conducted in other areas of orthopaedic surgery, similar studies should be conducted in the foot and ankle area to better guide appropriate management.

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QUESTION 2: What strategies can be implemented to help isolate the causative organism in patients with infection of the foot and ankle?

RECOMMENDATION: Transfer of synovial aspirate in blood culture bottles, obtaining deep biopsy of tissues and bone, obtaining multiple samples, increasing incubation period of cultures and the use of molecular techniques for culture negative cases are some of the strategies that can help improve the ability to isolate the causative organism(s) in infections of foot and ankle.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Given the risk of false positive cultures, it is important to holistically evaluate patients who are suspected to have an infection of the foot and ankle following an algorithm suggested by the Musculoskeletal Infection Society's definition of periprosthetic joint infection (PJI) [1]. It should be noted that these diagnostic criteria have not been evaluated for infections of the foot and ankle. Isolation of the causative organism in orthopaedic infections can be challenging. Culture-negative infections in hip and knee arthroplasty are not uncommon. Using the experience gained from hip and knee arthroplasty surgery and relying on the literature from the same field of orthopaedics, the following strategies may be implemented to improve the yield of culture in foot and ankle infections.

Synovial Aspirate

Synovial aspiration provides a variety of opportunities for testing, including synovial leukocyte esterase (LE) testing, synovial fluid white blood cell (WBC) count and polymorphonuclear (PMN) percentage, alpha-defensin levels, and Gram stain and cultures. In the hip and knee literature, application of synovial fluid to a simple urine test strip evaluating leukocyte esterase levels can be an accurate marker of PJI (sensitivity of 81-93%, and specificity of 87-100%) [2–4]. False positives do occur, and a positive LE strip should not be used in isolation to diagnose PJI. Although specific levels of synovial fluid WBC count and PMN percentage have been reported for diagnosis of PJI in the hip and knee, there is no literature specific to the foot and ankle [5–10]. Although alpha-defensin has been evaluated and is a promising new serologic test in the hip and knee, there is no literature to support its utility in evaluating infections of the foot and ankle [11,12]. While there is currently no literature defining criteria concerning LE, synovial fluid WBC and PMN percentage, or alpha-defensin levels for acute or chronic infection in the native or prosthetic ankle or soft tissue of the foot and ankle, we must use clinical suspicion and abnormal levels established by the adult hip and knee PJI literature until further studies evaluate abnormal levels in the foot and ankle. Several studies have demonstrated low sensitivity with Gram stain testing and poor utility for the diagnosis of PJI [13–15]. However, Gram stain and culture may provide additional information concerning likely causative organism and may help corroborate culture results with Gram stain findings in instances of potential contamination. There is no literature concerning the utility of Gram stain testing in the infected foot or hindfoot, and further studies may be necessary to better understand whether Gram stains aid in the diagnosis or treatment of suspected ankle or hindfoot native infection or PJI.

Blood Culture

Given the role of medical management in PJI with sepsis or bacteremia as well as prognosis, we recommend routine blood cultures for patients with systemic manifestations of infection. Although bacteremia is acknowledged as an etiology of PJI, the role of blood cultures in the diagnosis of PJI remains unknown. Currently, most guidelines state that blood cultures can be considered in light of systemic manifestations of infection but are not routinely obtained [16,17].

However, the care of patients diagnosed with PJI involves a multidisciplinary team, including infectious disease, internal medicine, emergency medicine and critical care physicians. Blood cultures are a staple in the work-up of many other medical conditions and may be acquired by the treating surgeon or more often a collaborating physician. Klement et al. investigated the role that blood cultures play in PJI patients and what association a positive result has on treatment outcome [18]. Blood cultures were obtained from 53.1% of patients (170/320) presenting with PJI at the time of diagnosis, with the same organism being identified 86.0% of the time in both blood and operative cultures. Furthermore, patients with positive blood cultures demonstrated a decreased treatment success rate compared with those with negative blood cultures. Therefore, the presence of positive blood cultures at the time of PJI diagnosis may not only impact the medical management of patients but also serve as a prognosticator towards the likelihood for success.

Tissue vs. Swab Culture

We strongly recommend against the routine use of swabs for surgical culture. In a study of 156 aseptic and septic hip and knee revision arthroplasties, Aggarwal et al. demonstrated that tissue cultures were positive in a higher percentage of septic cases than swab cultures: 28 of 30 (93%) versus 21 of 30 (70%). Surprisingly, tissue cultures were positive in two of 87 aseptic cases (2%), while swab cultures were positive in 10 of 87 (12%) [4]. Tissue cultures demonstrated higher sensitivity, specificity, positive predictive value, and negative predictive value for diagnosing PJI than swab cultures, while swab cultures had more false-negative and false-positive results than tissue cultures [4]. Because swab cultures pose a greater risk of failing to identify or incorrectly identifying causative organisms in PJI, we believe the use of swab cultures in obtaining intraoperative culture specimens should be discouraged.

Number of Intraoperative Samples

We recommend obtaining multiple intraoperative tissue samples for culture in suspected PJI cases or infections of the foot and ankle. Historic hip and knee protocols for periprosthetic tissue collection have been established with a target of five samples [19–21].

However, sensitivity and specificity are maximized with five to six periprosthetic samples being collected [13]. Given the relative difference in the surgical field area in hip and knee versus foot and ankle procedures, culture specificity and soft tissue preservation should not be compromised by taking more than six samples.

Holding Preoperative Antibiotics

We recommend routine holding of perioperative prophylactic antibiotics in all cases with a high suspicion for PJI in which a causative organism has not been isolated. There is mixed literature related to whether routinely holding antibiotics prior to surgery is necessary with no literature specific to foot and ankle. Recent antibiotic administration has been shown to decrease tissue culture sensitivity [22]. However, two prospective (one randomized) studies have demonstrated that prophylactic preoperative antibiotics do not impair the sensitivity of traditional intraoperative cultures [23,24]. Therefore, mandatory withholding of prophylactic antibiotics is not justified in cases where the pathogen has already been isolated preoperatively. Special consideration should be taken into account in cases in which PJI is diagnosed or suspected, but a pathogen has not been identified. In these cases, the use of prophylactic antibiotics is dependent upon clinical judgment.

Frozen Section

Intraoperative frozen section (FS) histopathology should be considered a valuable adjunct to the diagnostic work-up for patients undergoing revision arthroplasty in culture-negative PJI when the potential for infection remains following a thorough preoperative evaluation, but limitations should be noted. An intraoperative FS looking for acute inflammatory neutrophils in tissue obtained from the joint capsule or periprosthetic membrane has been used for intraoperative decision making. Although multiple studies have demonstrated that intraoperative FS of periprosthetic tissues performs well in culture-positive PJI with relatively high specificity, FSs lack the ability to isolate the organism and consistently demonstrated poor sensitivity and ability to rule out this diagnosis [25–29]. The optimum diagnostic threshold (number of PMNs per high-power field (HPF)) required to distinguish PJI from aseptic failure ranges from 5 to 23 with no clear threshold [30–32]. Although the appropriate thresholds for diagnosing PJI in histological analysis is controversial, a maximum tissue concentration between 5 to 10 PMN/HPF in each of 5 or more HPF seems to carry the best diagnostic performance. Neutrophils entrapped in superficial fibrin are not predictive of infection and submitting samples obtained by sharp dissection instead of cautery will help limit false positive diagnoses due to thermal artifacts.

Atypical Cultures – Acid Fast Bacilli (AFB) and Fungal

Mycobacterium and fungi are rare causes of PJI [33–35]. We recommend against routine AFB and fungal testing in suspected septic or aseptic failure except when warranted by patients who are at risk for such infections or when other traditional pathogens have not been identified where clinical suspicion remains elevated. Evidence has demonstrated that routine AFB and fungal testing in presumed aseptic cases does not yield clinically important results nor is it cost-effective [36]. However, when mycobacterium and fungal organisms are considered, AFB and fungal-selective media must be included, and it should be noted that prolonged culture may be required according to national laboratory standards. One should expand diagnostic testing to include tissue samples for histological examination, especially in patients with high clinical suspicions of infection. Resistance of Candida species to fluconazole has been reported in the literature, and susceptibility testing may be requested when resistance to fluconazole is suspected based on isolated species. Antifungal susceptibility testing remains less well developed and utilized than antibacterial testing.

Culture Incubation Period

We recommend that routine cultures be maintained for 5 to 14 days. If PJI by low virulence organisms is suspected, preoperative cultures failed to demonstrate bacterial growth, or if the clinical picture is consistent with culture-negative PJI, the cultures should be maintained for at least 14 days. Evidence demonstrates that extending periprosthetic cultures to two weeks significantly increases culture sensitivity while not increasing the risk of contaminants [21,37–39]. However, we recommend holding cultures for only five days in patients in whom the causative organism has been isolated preoperatively.

Routine Sonication of the Prosthesis or Implants

We are unable to recommend for or against the routine utilization of sonication of explants. The consideration of its use should be limited to cases with high suspicion for PJI or proven PJI cases in which preoperative aspiration fails to yield positive culture. Explant sonication utilizes ultrasonic energy to a fluid immersed sample to dislodge bacteria embedded in biofilm and has been shown to increase the likelihood of isolating pathogens without increasing the risk of contaminants [40–46]. Several studies have demonstrated better efficacy in dislodging bacteria from biofilm on titanium or stainless steel implants and improved sensitivity of cultured samples compared to scraping with a surgical blade [42]. In the hip and knee arthroplasty literature, Trampuz et al. demonstrated that sonication increases the rate of positive cultures and the sensitivity of sonicated fluid to identify that a causative organism was superior to that of tissue culture (78.5 vs. 60.8%) [40]. Similarly, Holinka et al. and Shen et al. found sonicate fluid to have a sensitivity greater than tissue (83.3 vs. 72.2%) as well as synovial fluid (88 vs. 64%), respectively [47,48]. When comparing sensitivities of cultures from sonicated fluid versus tissue samples, Yano et al. identified a sensitivity of 90.4 vs. 56.8%, respectively, in a large cohort of 180 fracture fixation explants [49]. In a mixed cohort of explanted joint prostheses and fracture fixation explants, Portillo et al. demonstrated improved sensitivity of cultures with 100 vs. 87 vs. 59% following inoculation of sonicated fluid in blood culture bottle compared to regular culture of sonicated fluid and tissue cultures, respectively [50]. The sonication of explants is an expensive procedure that is likely not justified in most assumed aseptic cases. In a large prospective study, the greatest benefit of explant sonication over standard tissue culture was found when antibiotics were provided within two weeks of surgery [41]. Although early literature is promising with possible greater sensitivity and improved bacteria detection with sonication, more literature is necessary to demonstrate the clinical efficacy and relevance prior to supporting broad utilization in the foot and ankle.

Fluorescence In-situ Hybridization (FISH)

We recommend against the routine use of FISH in order to evaluate for suspected infection of the foot and ankle. This process utilizes fluorescent probes to stain bacterial ribosomal ribonucleic acid, thus allowing direct visualization of the organisms in a native biofilm. Although FISH techniques have proven to be a highly reliable nonculture method to demonstrate the presence of pathogens even in the presence of biofilm, this technique is limited by its inability to provide speciation or antimicrobial susceptibility testing on the identified organisms [51,52].

Polymerase Chain Reaction (PCR)

We recommend against the routine use of nucleic acid-based testing for diagnostic testing for infection of the foot and ankle. In limited cases with high clinical suspicion of infection but negative cultures, PCR may help identify the unknown pathogens or antibiotic sensitivity. Although PCR techniques have proven to be more sensitive than traditional techniques, the number of false-positive results, as well as cost and availability of this technology, preclude routine screening. PCR should be reserved for limited cases with high clinical suspicion but negative cultures [53,54].

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QUESTION 3: What is the optimal method to perform bone biopsy (method, location, imaging use) for patients with foot and ankle infections?

RECOMMENDATION: A bone biopsy should generally be performed in a percutaneous fashion, particularly in cases where surgical debridement is not considered necessary.

If surgical debridement is considered necessary, then an open biopsy can be performed as part of the debridement.

Percutaneous biopsy should be performed under sterile conditions by an interventional radiologist or other physician trained in image-guided techniques.

The location of the biopsy will depend upon the clinical and radiographic evaluations, with a goal of maximizing the yield of the biopsy while minimizing the risk of injury to surrounding and/or overlying soft tissue structures.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infection in the foot and ankle bone or soft tissues can be associated with significant morbidity and even mortality. Prompt diagnosis and treatment are paramount. Often, diagnosis can be made based on a combination of clinical examination, radiographic imaging and laboratory data. Bone biopsy is considered the gold standard for the diagnosis of osteomyelitis [1–5].

Bone biopsy can be particularly helpful when the clinical exam, radiographic imaging and laboratory data are not clearly confirmatory of an underlying infection. Additionally, a bone biopsy can allow for identification of the infecting organism(s), and therefore allow for a more tailored treatment regimen. It can also exclude rarer causes of bone disease, such as malignancy or osteonecrosis [6,7].

A percutaneous bone biopsy is generally preferable to an open biopsy, particularly in cases where surgical debridement is not considered necessary. Percutaneous techniques are less invasive, less costly and are associated with less morbidity [7–10]. A percutaneous bone biopsy should be carried out under image guidance, generally either fluoroscopy or computed tomography (CT) and should be performed by an interventional radiologist or other physician trained on image-guided techniques. Image guidance allows for specimens to be obtained from specific targeted areas. The choice of imaging technique used to guide the biopsy depends on the anatomic location, availability and practitioner preference. Fluoroscopy can be used for more superficial lesions and allows for real-time guidance. Its main limitation is its two-dimensional nature. CT guidance provides visualization of not only osseous structures but also important soft tissue structures, such as neurovascular structures, within a three-dimensional framework. Its main limitation is the increased radiation exposure in comparison to fluoroscopy. There are reports in the literature regarding magnetic resonance (MR) guided percutaneous bone biopsies, but the availability of MRI-compatible instruments and accessories limits its use [11,12].

The choice of anatomical region to perform a biopsy will depend on the state of the overlying soft tissues and the radiographic findings. The goal should be to increase the yield of the biopsy while minimizing potential risk to nearby soft tissue structures. In general, more superficial areas of concern are targeted. If multiple areas of concern exist, one will also want to prioritize the site which is likely to provide the highest diagnostic yield. The procedure should be performed under sterile conditions to reduce the risk of contamination of skin flora. If possible, multiple samples should be obtained utilizing multiple trajectories within the bone to increase the diagnostic yield of the procedure.

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QUESTION 4: What is the best method to differentiate acute Charcot foot from acute infection?

RECOMMENDATION: Differentiation between acute Charcot neuroarthropathy (CN) and acute infection/osteomyelitis is complex and requires multiple (>1) diagnostic criteria. These criteria include an emphasis on the presence of neuropathy, history and physical examination. The absence of skin wounds and resolution of swelling/erythema with elevation makes the likelihood of infection very low.

In unclear cases, laboratory testing, histological examination and culturing of bone specimens, scintigraphy, and imaging, especially magnetic resonance imaging (MRI), may be of benefit.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

At initial presentation, acute infection comprising of cellulitis and osteomyelitis (OM) and CN may be difficult to differentiate. However, it is important for the clinician to make an accurate diagnosis, as correct treatment largely determines outcome as both present a substantial risk of limb amputation and mortality.

Physical features can provide essential clues to the diagnosis. The "probe-to-bone" test, which tests whether the underlying bone is palpable via a probe inserted into a wound, has demonstrated sensitivity ranging from 38 to 95%, specificity ranging from 84 to 98%, and a positive predictive value ranging from 53 to 97% for the diagnosis of osteomyelitis [1–6]. In their study of 1,666 consecutive diabetic patients, Lavery et al. demonstrated that a positive probe-to-bone test increases the probability of OM greater than 50%, whereas a negative test is a strong predictor of absence of infection [3]. The test, however, has shown to have a high variability when performed by inexperienced clinicians, but this intra-observer variability was demonstrated to decline with experience [7].

In terms of other physical features, CN typically affects the midfoot and lacks associated skin breakage, whereas OM is more frequently found in the forefoot and is often accompanied by soft tissue infection or ulcer [8,9]. Additionally, while it is possible to contract OM through hematogenous spread, the vast majority of cases are spread directly via a soft tissue infection or ulcer. A wound size > 4.5 cm^2 is associated with a three times higher chance of underlying OM [10]. However, others have suggested that both ulcers of size > 2 cm^2 and depth > 3 mm are also significant [11,12]. White blood cell (WBC) counts, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are often utilized for work-up of infection. Some investigators have concluded that elevated ESR (> 70 mm/h) is strongly associated with OM [11–14].

A further benefit of ESR is that, while levels of the other inflammatory markers drop rapidly once antimicrobial treatment begins, ESR remains elevated for longer periods of time, therefore making it useful in monitoring treatment efficacy. Interleukin (IL)-6 has also been suggested as a marker for diagnosis of OM and monitoring treatment in preliminary studies [15,16]. However, these inflammatory markers are nonspecific and may be elevated by various other factors. Given that many patients with histologically proven OM may present with a normal WBC count, hematologic studies alone are not reliable for diagnosis of OM [11–14].

Bone culture alone is reported to have a sensitivity of 92% and a specificity of 60% in diagnosing OM in diabetic feet [17]. Bone samples can be obtained by percutaneous biopsy or during surgery [12,18]. However, bone specimens may often yield false-positive or false-negative results. Histologic analysis is suggested to be important in preventing these undesirable results, as several studies have shown that 40 to 60% of histologically proven cases of OM at surgery or biopsies of foot and ankle had negative cultures [19–22]. Therefore, standard criteria for the diagnosis of OM should be a positive culture with histopathologic evidence of infection in bone specimen [23].

Radiographic signs of infection, such as demineralization, periosteal reaction and cortical destruction, may not appear until two to three weeks after onset and require a loss of 40 to 50% bone mass to detect the difference [8,24]. The accuracy of plain radiography for early diagnosis is 50 to 60% with a sensitivity of 60% and a specificity of 80% [25,26]. Therefore, more advanced imaging is needed for diagnosis of acute osteomyelitis.

Magnetic resonance imaging (MRI) is suggested to be an effective modality to aid in early diagnosis [27,28]. A previous meta-analysis has shown that the sensitivity of MRI to diagnose OM in the foot and ankle is 90% sensitive and 79% specific [29]. In a meta-analysis of 16 studies, MRI performance was superior to that of technetium ^{99m}Tc bone scanning, plain radiography, and WBC studies. The sensitivity for the diagnosis of OM was found to be 90% while specificity was 85% [30]. MRI was better able to identify the extent of the involved area, whereas WBC bone scan may have better performance in differentiating OM from CN, especially in patients with metal implants [23,24].

While chronic CN shows low intensity in both T1- and T2-weighted images, both acute OM and acute CN show low signal on T1-weighted images and hyperintensity on T2-weighted images with contrast enhancement. However, these are common markers in both infective and neuropathic disease, making differentiation

of the two difficult [31]. OM almost always follows surrounding soft tissue infection, therefore identifying soft tissue edema, ulceration, or sinus tracts on imaging would suggest infection. MRI findings of diffuse bony edema in bony prominences (calcaneus, metatarsal heads, malleoli) and phalanges, with a contiguous spread would also suggest OM [32–34]. CN typically shows periarticular and subchondral changes (including fractures) as the pathology centers around the joint [35]. Disease affecting one or multiple joints, in particular of the midfoot, would also suggest CN [35].

Aside from MRI imaging, three-phase bone scintigraphy has a high sensitivity (80 to 100%) but poor specificity (25 to 60%) in diagnosing OM [36]. Labeled leukocyte scans (tagged WBC scans) are similarly sensitive, but more specific [23]. Capriotti et al. reported 86% sensitivity and 85% specificity for ^{99m}Tc-labelled leukocyte scintigraphy [37] and Dinh et al. reported that a ^{111}in-labelled leukocyte scan had a sensitivity of 74% and specificity of 68% [29]. Fluorodeoxyglucose (FDG) positron emission tomography (PET), which measures increased intracellular glucose metabolism, has demonstrated promise in diagnosing CN, particularly with regards to negative predictive value. Basu et al. found sensitivity and specificity of FDG PET in the diagnosis of CN to be 100% and 93.8%, both higher than the corresponding values of 76.9% and 75% for MRI [38]. Study results are inconclusive, however, with some authors finding that its use is limited when compared to MRI and WBC scintigraphy [39,40]. Further interesting developments in aiding in diagnosis are PET-computed tomography (CT) and PET-magnetic resonance (MR), which show promising early results [41–43]. Rastogi et al. reported the sensitivity and specificity of FDG PET-CT to be 83.3% and 100%, compared with 83.3% and 63.6% for contrast-enhanced MRI for the diagnosis of diabetic foot OM in the background of CN [41].

Previous systemic reviews of the literature (including the International Working Group on the Diabetic Foot's consensus scheme for the diagnosis of diabetic foot OM) and meta-analyses have proposed specific criteria for differentiation of CN from OM [21,23]. The proposal was based on using post-test probabilities to define broad levels of diagnostic certainty, with OM most likely being present if (1) a bone sample shows positive culture and is confirmed with histopathology, (2) intraoperative finding shows purulence in the bone, (3) intraosseous abscess is found on MRI or (4) exposed bone exists in the foot ulcer with corresponding changes in advanced imaging. However, the validity of the criteria has not been clinically tested and should, therefore, be utilized with caution.

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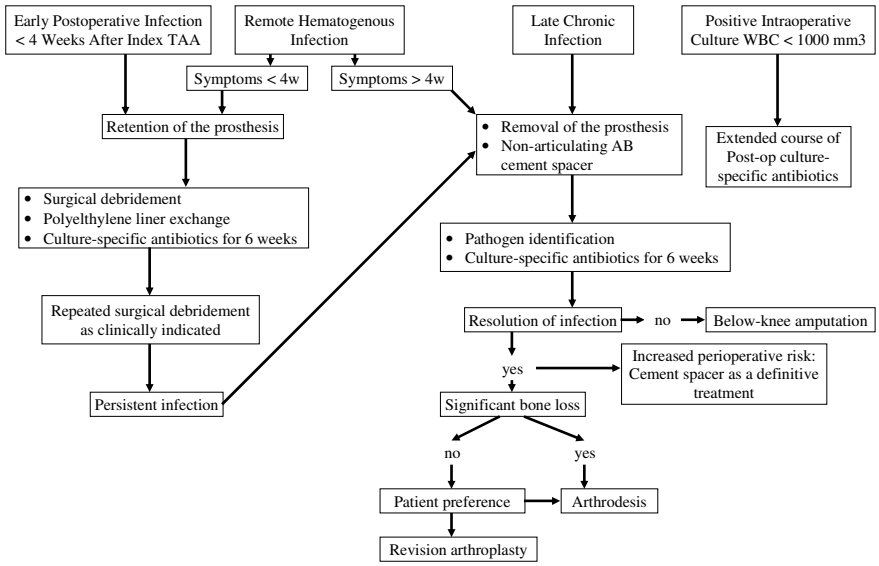
Treatment

3.1. TREATMENT: TOTAL ANKLE ARTHROPLASTY-SPECIFIC

Authors: Steven Raikin, Selene Parekh, Elizabeth McDonald

QUESTION 1: What is the treatment "algorithm" for an infected total ankle arthroplasty (TAA)?

RECOMMENDATION: The treatment of an infected TAA is largely dictated by the acuity of the infection. The following treatment algorithm modified for TAA is recommended [1].



LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The reported rate of infection after TAA is between 0 to 5% [2–4]. The management options are based on the time of presentation after index TAA and the duration of infection symptoms. It is a common practice to attempt to retain the ankle prosthesis when the infection is acute, particularly when it occurs during the early postoperative period. There are a number of treatment options available for infected TAA that includes surgical debridement, retention of the prosthesis and administration of intravenous antimicrobial therapy (DAIR), one or two-stage exchange arthroplasty, arthrodesis or amputation.

TAA infection literature cautions that great attention should be paid to delayed wound healing and its association with infection [5–10]. van der Heide et al. reported on the outcome of 58 TAAs in 51 patients with underlying rheumatoid arthritis (RA) or juvenile inflammatory arthritis (JIA) who had Buechel-Pappas or STAR implants [5]. Among this cohort, three patients (5%) developed early surgical site infection (SSI) and one of three (33%) patients treated with the van der Heide SSI protocol went on to develop a deep infection. The SSI protocol involved exploration of the surgical site, debridement of the wound and administration of systemic and local antibiotics. The ankle that developed deep infection underwent resection of the implant and subsequent fusion at six months. Further, Patton et al. reported on 29 cases of infected TAA and noted that 9 of the 29 (31%) infected TAAs were cases of delayed surgical wound healing that went on to deep infection [6].

Irrigation and debridement (I&D) can be a key first-step treatment of early TAA infections (early being defined as less than four weeks from the index TAA or remote hematogenous infection with symptoms less than four weeks) [7,11,12]. In a level III prognostic study, Kessler et al. defined infection parameters and proposed a treatment algorithm [7]. They selected 26 patients with PJI of TAA and matched patients with two control groups with 52 patients in each group. From this prognostic study, Kessler et al. proposed a diagnostic criteria for TAA infection which was based on presence of clinical

signs of pain, effusion, erythema and induration as well as one of the following criteria: (1) same microorganism growth in two or more cultures of synovial fluid and/or periprosthetic tissue, (2) visible pus surrounding the joint, (3) acute inflammation upon histopathological examination (greater than or equal to 10 neutrophils/high-power field) or (4) the potential to probe the base of a wound at the implant. They defined exogenous cases as locally acquired through the wound and hematogenous cases had an uneventful postoperative course for a minimum of *three months* after the initial TAA and/or there was a distant infection source. Four of 26 (15%) TAA infections were hematogenous in origin, and 22 of 26 (85%) TAA infections were exogenous. Meanwhile, *Staphylococcus aureus* and then coagulase-negative staphylococci were the most common pathogens. When compared to the control, risk factors for developing deep infection included persistent wound dehiscence (odds ratio (OR) = 15.38, 95% confidence interval (CI) = 2.91 to 81.34, p = 0.01, in comparison with both control groups) and secondary wound drainage (OR = 7.00, 95% CI = 1.45 to 33.70 in comparison with the age/sex-matched group and OR = 5.31, 95% CI = 1.01 to 26.78 in comparison with the time-matched group, p £ 0.04).

The TAA literature reports upon the success of irrigation and debridement (I&D) in early postoperative cases. Mann et al. reported on 84 ankles in 80 patients with a mean follow-up of 9.1 years with a 3 in 84 (3.5%) incidence of deep infection [10]. All deep infections were exogenous and occurred immediately postoperatively as a result of incomplete wound healing. Mann et al. treated all deep infections with open debridement and six weeks of intravenous antibiotics. One of the deep infections required a local skin graft and another required a free vascularized tissue flap for closure. No metallic prostheses were removed and there was no evidence of recurrent infection with an average follow-up of 9.3 years [10]. These results demonstrate the success of early debridement. Further demonstrating the success of I&D amongst exogenous cases, Nodzo et al. reported on 75 ankles with Salto Talaris prostheses. One of the 75 (1.3%) went on to develop deep infection within the first three weeks following TAA [11]. The patient was treated with I&D and intravenous antibiotics and the patient retained all components. Similarly, Borenstein et al. reported one ankle out of 65 consecutive TAAs (1.5%) that experienced deep infection [12]. The patient was treated with I&D and six weeks of intravenous antibiotics. Additionally, Patton et al. demonstrated the merits of I&D in detailing 29 cases of infected TAA [6]. If an I&D and revision arthroplasty were performed, 23 of 29 (79%) limbs were salvaged. Meanwhile, if revision TAA alone was performed, 19 of 29 (65%) TAA retention was reported.

In addition to I&D, the literature details the effectiveness of polyethylene liner exchange in cases of early postoperative infection and remote hematogenous infection when symptoms extend for less than four weeks [14–17]. Claridge et al. responded to the 2 of 28 (7%) cases of deep infection with polyethylene exchange only [13]. Similarly, Stoodley et al. detailed polyethylene liner exchange as an important early treatment step [16].

Reports on revision TAA after deep infection are variable [15,16,18–21]. In a case report describing TAA infection after a routine dental procedure, Young et al. described the work-up, blood cultures positive for *Streptococcus mitis* and a 6-week course of antibiotics with penicillin G and 18 million units intravenously daily for one additional week [17]. The patient remained non-weightbearing in a CAM boot until revision TAA surgery at three-months post-infection. Good outcomes with the patient walking pain-free at 16-month follow-ups were recorded. While Sproule et al. also opted for a revision TAA to treat the 1 of 88 (1%) for deep infection, they opted for a two-stage revision and recounted successful results [18]. Further reports of metal component revision after deep infection TAA demonstrated good results [15,19].

In a retrospective case series on 613 TAA, the 19 cases of deep infection were treated by established algorithms depending on if they were exogenous or late chronic infection [14]. For exogenous infection, Myerson et al. attempted prosthesis retention for 4 of 19 (21%) implants. Three (16%) had early post-op infections at three, five and seven weeks following initial implantation. All had I&D plus polyethylene liner exchange and later antibiotic therapy. One (5%) had an acute hematogenous infection. In this strategy, all four patients had recurrent infection and went on to require removal of the implant and staged treatment. Meanwhile, 15 of 19 (79%) deep infections in this series were late chronic infections. Of the deep infections, seven revision TAA were attempted but only three (16%) were successful. Of the four that failed revision TAA, three had recurrent infection and one aseptic loosening. Otherwise, for successful revision surgery, six patients were converted to arthrodesis; seven patients had a permanent antibiotic spacer, and three patients underwent transtibial amputation. The mean time to revision TAA or arthrodesis following initial infection treatment was 7.8 months (range, 2.5 to 13 months).

Revision TAA after late chronic infection has no consensus, and others advocate for conversion to arthrodesis in the case of infected TAA [8,15,22–25]. As reported by Myerson et al., six patients converted to arthrodesis all had successful revision, but only three of seven (43%) TAA revisions were successful [14]. Additionally, McCoy et al. reported on three failed TAAs due to infection [22]. These patients were revised using circular external fixator-assisted ankle arthrodesis and distraction osteogenesis for limb length equalization. All patients reported solid pain-free fusion and good subtalar joint alignment. Further evidence of good results, Mulhern et al. recounted the successful conversion to tibiotalocalcaneal arthrodesis with custom titanium alloy truss and retrograde intramedullary nail after revision TAA polyethylene became infected with *Staphylococcus aureus* [23]. Devries et al. added evidence to support arthrodesis instead of revision TAA after infection [24]. In their case series of five revision TAAs, Devries et al. initially converted the one deep infection directly to a revision TAA. While the deep infection was cleared at the time of replacement, the revision TAA went on to develop an infection. After failing two courses of long-term IV antibiotics, an antibiotic spacer was implanted and later converted to a tibiotalocalcaneal arthrodesis.

However, if deciding to proceed with a revision TAA after deep infection, there is evidence to support that single hydroxyapatite component coating should not be used in the revision [25]. When examining 117 consecutive ankles in which TAA failed after mean 4.3 years, Hinterman et al. found that 9 of 117 (8%) TAAs failed due to infection [26]. Avoiding single hydroxyapatite component coating, the group reported that the custom long-stemmed talar implant had good results amongst revisions with a 100 in 117 (85%) success rate, and one revision TAA attributed to deep infection.

While wound closure for deep infection is a coordinated effort with plastic surgery, plastics' perspective on wound closure for infected TAA is valuable when discussing a TAA infection algorithm. Goldstein et al. reported on two infected TAA treated for random local flap for wound coverage of the ankle [9]. Patients presented at a wound healing center for random local flap for wound coverage of the ankle. "Patient 3" required two flaps for infected TAA with lateral ankle wound: one peroneus longus muscle flap with hardware as exposed structure and one fasciocutaneous transposition flap with fibula as the exposed structure. "Patient 3" required 4 total operations and had a 55-day follow-up with no resultant complications. Meanwhile, "Patient 9" required two flaps for infected TAA with lateral ankle wound: one lateral calcaneal artery fasciocutaneous flap with hardware as the exposed structure and one fasciocutaneous transposition flap with hardware as the exposed structure. "Patient

9" required 2 total operations and had a 75-day follow-up with no resultant complications.

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QUESTION 2: What is the optimal (type, dose and route of administration) antibiotic treatment for patients with infected total ankle arthroplasty (TAA)?

RECOMMENDATION: Though literature specific to TAA is lacking, based on recommendations for the management of hip and knee arthroplasties, the choice of antibiotic should be made based on the identification and sensitivities of the infecting organism(s). Dosing, frequency and route of administration of antibiotics may be determined in consultation with an infectious disease specialist and by taking into account the patient's weight and comorbidities, such as renal impairment and the antibiogram.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

There is a paucity of literature regarding the treatment and outcomes of periprosthetic joint infection (PJI) in TAA. The two largest studies on post-TAA infection from the United States report the use of six weeks of intravenous (IV) antibiotic therapy following surgical treatment of the infection [1,2]. In a study from Europe, Kessler et al. reported the use of one to two weeks of IV antibiotics followed by three months of oral antibiotics following surgical treatment for infection [3]. In all of these studies, the choice of antibiotic(s) was made based on the identified infecting organism(s) and its antibiotic sensitivity and with the assistance of an infectious disease specialist. In general, the most common pathogens responsible for PJI are *Staphylococcus aureus* (methicillin-susceptible or -resistant), coagulase-negative Staphylococci and other constituents of the skin's bacterial flora [4,5].

The timing of PJI following TAA is also important in determining infection management. If the infection developed within 6-12 weeks of implantation, this is considered an acute infection and debridement with retention of the implants (DAIR) and antimicrobial treatment are the most desirable approach. Conversely, for a device that has been present for more than three months, a chronic infection is presumed to be present, and a one- or two-stage exchange with antimicrobial treatment is the desired course of action [5–7].

In the hip and knee literature, there has been a debate with regards to the duration of antibiotic treatment. Some studies have recommended as many as three to six months of antimicrobial therapy following surgical intervention, depending on the organism [6,8]. However, other studies have shown six weeks of IV antibiotics to be a sufficient duration of treatment [9–11].

The theoretical benefit of a shorter course of antibiotics, aside from patient convenience, includes a reduced risk of adverse drug events (ADEs), including anaphylaxis, nephrotoxicity, hepatotoxicity and infectious colitis, as well as bacterial resistance [12]. The International Consensus on Periprosthetic Joint Infection stated that the duration of antibiotic therapy following removal of implants is inconclusive but recommended a period of antibiotic therapy between two to six weeks [13].

The authors of the Infectious Diseases Society of America (IDSA) Guidelines for the Diagnosis and Management of Prosthetic Joint Infection make the following recommendations for the management of hip and knee arthroplasties while suggesting that similar recommendations can be extended for the management of TAA infections [6]. The IDSA recommends four to six weeks of pathogen-specific IV or highly bioavailable oral antibiotic therapy following removal of implants, regardless of organism or in non-staphylococcal PJI treated with DAIR. They recommend two to six weeks of IV antibiotics in combination with oral rifampin, followed by 3 months of rifampin plus a companion oral antibiotic for a staphylococcal TAA PJI treated with DAIR. If rifampin cannot be used because of an allergy or toxicity concern, the IDSA recommends four to six weeks of IV antibiotic therapy. Of note, the IDSA recommendations are the same in the setting of a one-stage exchange as they are following DAIR [6].

Further studies on the treatment and outcomes of infection in TAA are needed. For now, we must rely on the hip and knee arthroplasty literature as well as the recommendations of the MSIS and IDSA.

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QUESTION 3: Is there a role for suppressive antibiotics in patients with perioperative joint infection (PJI) of total ankle arthroplasty (TAA) who have undergone surgical treatment?

RECOMMENDATION: Culture-directed antibiotic therapy is recommended for patients undergoing surgical treatment of infected TAA. Routine administration of suppressive antibiotics in patients with an ankle prosthesis in place is not warranted; however, in certain clinical circumstances, this may be of benefit.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

There is scant literature related to the management of infected TAA. The available reports have been reviewed to determine if there is a role for routine administration of suppressive antibiotics after surgical management of infected TAA. The published studies do not address the issues of suppressive antibiotic therapy after infected TAA.

Myerson et al. reported on 19 patients with infected TAA [1]. In early acute infections, patients were treated surgically with irrigation and debridement (I&D) and polyethylene exchange, followed by six weeks of antibiotics. Of the four patients treated with this approach, all had persistent infections and required prosthesis removal. No comment was made regarding suppressive antibiotics after staged revision for infection. Patton et al. reported on a series of 29 TAA infections [2]. Acute infections were treated with polyethylene exchange and I&D. Of 14 acute infections, only three were treated successfully with this approach. Again, no comment was made regarding suppressive antibiotics after staged revision.

There is also little related to this question in the hip and knee literature. A recent study supported by The Knee Society evaluating this issue after surgical management of infected TAA found that

administration of suppressive antibiotics after reimplantation of the knee in patients undergoing two-stage exchange arthroplasty resulted in lowering the rate of subsequent failure [3]. The authors of the study stated that the findings were preliminary and further long-term data on the cohort was needed.

There are many potential issues related to administration of routine suppressive antibiotic therapy after surgical management of infected prosthetic joints. Cost, the potential for emergence of antimicrobial resistance, systemic adverse effects and so on are some of these potential issues. Therefore, and in the absence of concrete data, we believe that routine administration of suppressive antibiotic therapy for patients with a prosthetic ankle joint in place is not warranted. We realize that patients with infected TAA need to be treated on an individual basis and administration of oral antibiotics to some patients, such as those with extensive comorbidities, those infected with resistant organisms and those with complex infections may be justified in some circumstances.

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QUESTION 4: What determines the type and dose of antibiotic that is needed to be added to the cement spacer in patients with infected total ankle arthroplasty (TAA)?

RECOMMENDATION: We recommend tailoring the antibiotic in cement spacers to the infecting organism if it has been identified, as is typically done in total knee and hip arthroplasty. Otherwise, broad-spectrum antibiotics may be utilized. Medical comorbidities should always be considered, especially with regard to renal function and allergy profile. A thermostable antibiotic should be added to cement.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

TAA is performed much less frequently than total hip and knee arthroplasty, and reports related to deep infections and associated management are limited.

Like hip and knee arthroplasty, management of infected TAA may include removal of prosthesis and insertion of an antibiotic-impregnated cement spacer. An antibiotic spacer, as part of two-stage exchange arthroplasty, has been utilized in the management of infected TAA. Lee et al. described the use of cement mixed with 1 gm gentamicin, 1 gm vancomycin and 1 gm cefazolin in nine patients with infected ankle joints, three of whom were status post TAA [1]. The infecting organisms of the three TAA patients included methicillin-resistant *S. aureus* (MRSA), methicillin-resistant *S. epidermidis* (MRSE) and *Enterococcus*. The authors utilized their technique with the intent of permanent spacer use and a return to weightbearing, as multiple lower extremity operations have been associated with amputation.

Given the fragile soft tissue envelope around the ankle, Ferrao et al. also describe the use of a definitive antibiotic spacer after ankle infection [2]. Six of nine patients were status post-TAA and required explantation due to infection. The authors indicated that culture-specific antibiotics were mixed into cement when possible, although the detailed combination was not listed. If the infecting organisms were not isolated by culture, 2 gm vancomycin and 1.9 gm gentamicin were mixed into the cement. Bacteria were isolated in seven of the nine patients: *Staphylococcus aureus* (n = 3), *Staphylococcus epidermidis* (n = 3) and *Streptococcus viridans* (n = 1). Three patients required additional surgery, including two patients who underwent below-the-knee amputations.

In a large series including 966 patients, 29 patients were identified with infection after primary or revision TAA [3]. Cement spacers were placed in 17 cases, although the antibiotic formulation of the spacers was not indicated. The most common infecting organisms included methicillin-sensitive *S. aureus* (MSSA), coagulase-negative staphylococci and polymicrobial infection (one of which included MRSA).

Fifteen deep infections were identified in another series including 613 primary and revision TAAs at a single institution [4]. An additional four deep TAA infections from outside facilities were also treated during the study period. Antibiotic spacers formulated with 1 gm vancomycin and 1.2 gm tobramycin per cement packet were used for chronic infections requiring explantation. The infecting organisms included coagulase-negative Staphylococcus (n = 6), MSSA (n = 4), MRSA (n = 2), *C. acnes* + coagulase-negative Staphylococcus (n = 1), *E. coli* (n = 1), *S. viridans* (n = 1) and polymicrobial including MRSA (n = 1). Four attempted reimplantations were performed, but all subsequently failed due to infection with coagulase-negative Staphylococcus and MSSA.

Another study documented 26 TAA infections in a cohort of 408 patients at a single institution [5]. The most common infecting organisms included *S. aureus* (n = 8), coagulase-negative Staphylococcus (n = 8), *Enterococcus* (n = 4), polymicrobial (n = 4), *Enterobacter* (n = 3), *Klebsiella* (n = 2), *C. acnes* (n = 2) and MRSA (n = 1).

If the infecting organism is known prior to explantation based on preoperative aspiration, the use of tailored antibiotics incorporated into the cement spacer is recommended [3]. This has been recommended in total hip and knee replacement and can be extrapolated for use in the ankle [6,7]. Antibiotic-laden spacers result in higher antibiotic concentration at the infected site for a longer duration than that achieved with systemic antibiotics alone [8]. Tailoring the antibiotic selection is important to avoid breeding unneces-

sary resistance that has been identified after aminoglycoside-impregnated spacers [9].

Antibiotic selection requires consideration of a number of factors. Cultures from preoperative aspiration are informative; however, draining sinus cultures may have contaminating organisms [8,10,11]. Consultation with a microbiologist or infectious disease service may be helpful to determine an appropriate preparation for the cement spacer [12]. If no organism is identified, antibiotics with broad-spectrum coverage may be utilized [6,8,13,14]. One study showed effective eradication of infection with the use of 2 gm vancomycin, 2 gm gentamicin and 2 gm cefotaxime per 40 gm packet of cement for broad-spectrum coverage [7]. This combination is effective against MRSA (vancomycin), gram-negative bacteria including Pseudomonas (gentamicin) and gentamicin-resistant organisms (cefotaxime) [15].

When selecting an appropriate antibiotic profile for the cement spacer, factors to consider include thermostability, water solubility, patient allergy and availability as a sterile powder [7,16]. Some of the available options include gentamycin, vancomycin, ampicillin, clindamycin, tobramycin and meropenem [7,12,17]. Tobramycin is commonly used and has been shown to be stable during the exothermic reaction of cement mixing and elutes in high concentration to be effective against multiple common bacteria implicated in periprosthetic joint infection [18].

Combining antibiotics may result in higher local antibiotic concentration than individual antibiotics. Vancomycin combined with imipenem-cilastatin eluted higher concentrations of antibiotic and for a longer duration when compared to in vitro elution of vancomycin-impregnated cement alone [19]. Similar findings have been shown with vancomycin combined with tobramycin [20]. Tobramycin also has been shown to elute in higher concentration and for a longer duration than vancomycin [21]. Tobramycin, gentamicin and vancomycin are the most commonly used antibiotics, but others have been described and may be utilized depending on patient allergy profile, bacterial resistance and fungal infection [22].

The additive effect seen with certain antibiotics may be related to the higher solvent concentration in the cement that can diminish structural integrity but increase surface area for elution. To that effect, mixing the cement and antibiotic without vacuum assistance is theoretically superior since porosity is increased [23]. Palacos (Heraus; Wehrheim, Germany) cement seems to have a better profile for use than Simplex (Stryker; Mahwah, NJ) cement in multiple studies that show antibiotic elution in higher concentrations and for a longer duration [21,24–26]. In general, mixing more than 5 gm of additional powdered antibiotics into cement is not recommended because of its effect on the mechanical strength of the cement and potential for systemic toxicity [27]. Some antibiotics, such as rifampin, have been shown to interfere with cement curing and may not be ideal for use [28]. However, new technology with alternative delivery systems, like rifampin in microencapsulating in alginate beads, may allow broader coverage of infecting organisms as greater rates of antibiotic resistance emerge [28].

Common doses of antibiotics added to cement for treatment of periprosthetic joint infection are shown in Table 1. There are a wide variety of published quantities of antibiotics, with the trend generally going towards higher doses. However, a recent study demonstrated that higher dose antibiotics are not necessarily associated with the best elution properties; optimal in vitro antibiotic dosage in terms of elution rate and duration included tobramycin 3 gm and vancomycin 2 gm [29]. Vancomycin 2 gm per 40 gm packet of cement has been shown to meet the minimum inhibitory concentration (MIC) for five weeks after implantation [19,23]. Some antibiotics such as cefazolin, ciprofloxacin and ticarcillin, do not maintain adequate elution levels and are therefore less favorable for use [30].

TABLE 1. Antibiotic additives to cement for treatment of periprosthetic joint infections

Antibiotic	Activity Against	Quantity per 40g Cement Packet	Notes
Vancomycin-P	Gram-positive bacteria including methicillin-resistant organisms	2 gm [19,23]	
		4 gm	Studied in combination with ceftazidime 4 gm for broad-spectrum coverage [45]
Tobramycin	Gram-negative bacteria including *Pseudomonas*	2.4 gm [46]	
		4.8 gm [47]	
Daptomycin	Gram-negative bacteria	1 gm [25]	
Amikacin	Gram-negative bacteria and *staphylococcus*	1 gm [25]	
Clindamycin	Gram-positive cocci and anaerobes	6 gm [30]	
Imipenem/Cilastatin	Broad spectrum including gram-positive and gram-negative including *Pseudomonas* and *Enterococcus*	2 gm	Studied in combination with vancomycin 2 gm [19]
Ceftazidime	Gram-negative bacteria including *Pseudomonas*	4 gm	Studied in combination with vancomycin 4 gm for broad-spectrum coverage [45]
Amphotericin B	Fungal infections	100-150 mg [48]	

During the addition of antibiotics to cement, drug metabolism and concentration should also be considered. In addition, the medical comorbidities of the patient, such as renal function and allergy profile, should be considered, as these will influence the dose of antibiotics to be added to the cement and may preclude certain classes of antibiotics to be used. The incidence of acute kidney injury due to elution of antibiotics from a cement spacer has been reported to range between 4.8 and 20%, as aminoglycosides and vancomycin are both renally excreted [7,31–34]. Furthermore, a high concentration of certain antibiotics may be detrimental to local tissues and affect healing. Tobramycin can decrease cell growth if the concentration is greater than 400 micrograms/mL [35]. Gentamicin levels greater than 100 micrograms/mL have cytotoxic effects on osteoblasts, and this threshold is commonly exceeded for ten days after implantation of a spacer with gentamicin [36–38]. Vancomycin appears to be safe as long as the concentration is under 1,000 micrograms/mL [39].

Because of the risk of bacterial contamination may increase with time, the duration of an antibiotic spacer in situ should be limited. This is especially true if revision TAA is planned. The spacer may become colonized in 15 to 50% of cases, and the odds ratio of reinfection when positive culture is obtained from a cement spacer is eight times [40]. Recently, resistant bacteria have been identified on antibiotic-cement beads at the time of reoperation [41]. The antibiotic elution decreases over time, which reaffirms limiting the duration of spacer use [40,42–48].

Based on our understanding of the available literature, including much related to management of infected hip and knee arthroplasties, we recommend that 2 gm of vancomycin and 2.4 gm of tobramycin be mixed with every packet (40 gm) of methylmethacrylate cement to allow for coverage of a broad spectrum of organisms. In some infected TAA cases, additional or alternative antibiotics may be needed based on the identity of the infecting organism(s) and the antibiogram. Unless used as definitive treatment, the cement spacer should not be left in situ for too long because of the potential for the spacer to act as foreign material after antibiotic elution is completed (usually within a few weeks).

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QUESTION 5: What are the indications and contraindications for irrigation and debridement and retention of prosthesis (DAIR) in patients with infected total ankle arthroplasty (TAA)?

RECOMMENDATION: DAIR with polyethylene exchange may be indicated in early postoperative infection (< four weeks) or acute hematogenous infection (< four weeks of symptoms) in patients with infected TAA, although recurrent infection has been seen. Sufficient clinical evidence is lacking.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Periprosthetic joint infection (PJI) is a serious complication after TAA. Deep infection of TAA can be limb-threatening; hence, prompt treatment is required to minimize the potentially devastating effects of infection. Currently reported infection rates after TAA range from 1.1 to 8.5%, with reports indicating that newer anatomic designs have lower overall infection rates [1–6].

The current indications for DAIR in infected TAA include early postoperative infection and acute hematogenous infection. Myerson et al. retrospectively reviewed 572 TAAs over a 10-year period and found 19 cases of PJI (3.3%), including 15 chronic infections, three early postoperative infections, and one acute hematogenous infection [7]. The three early postoperative infections and one acute hematogenous infection were treated with initial irrigation and debridement with polyethylene liner exchange. All four cases resulted in recurrent infections that were treated with successful revision TAA, tibiolacalcaneal fusion and antibiotic cement spacer with an average retention time of six months. Only one case had an initial negative culture. The authors postulated that the inability to eradicate bacteria could be secondary to the ankle's unique anatomy with difficult access to regions such as the posterior gutters to perform a complete debridement. Additionally, Patton et al. reviewed 966 TAA over a 17-year period and found 29 cases of infected TAA (3.2%) [8]. They treated acute infections with polyethylene exchange in two cases and debridement alone in three cases. All five cases were apparently treated successfully with no evidence of subsequent failure.

There is paucity in the current literature regarding the management of PJI of TAA. Indications for DAIR are limited to early postoperative infection and acute hematogenous infection, and most guidelines are derived from the knee and hip studies. There are mixed results even in this selected group of patients, as all four patients with early infection from one study suffered persistent infection following DAIR, raising questions regarding the efficacy of this procedure. It is unclear at this point whether the failures stem from inadequate debridement due to the unique anatomy of the ankle or whether the natural history of ankle infection is inherently different than that of the hip and knee. Larger and additional studies are needed to provide a higher level of recommendation at this point.

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QUESTION 6: What is the optimal protocol for performing debridement, antibiotics and implant retention (DAIR) in an infected total ankle arthroplasty (TAA) (type and volume of irrigation solution, and so on)?

RECOMMENDATION: DAIR in acute TAA infections may be an acceptable treatment option. If performed, DAIR should be done meticulously, ensuring that all necrotic or infected tissues are removed and modular parts of the prosthesis, if any, exchanged. The infected joint should also be irrigated with antiseptic solutions.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

For total hip and knee periprosthetic joint infection (PJI), the DAIR procedure is a viable alternative to explantation or one-stage revision in cases of early infections by a relatively antibiotic-susceptible bacteria, in the absence of mechanical problems or a sinus tract. Concerning TAA infections, these general prerequisites for DAIR are not different than for other PJIs, but the success of DAIR in TAA infection is relatively poor (see Table 1). The best evidence is reported by Kessler et al. [1]. The authors investigated 34 cases of TAA infection, of which 21 were treated by DAIR. Remission using the DAIR procedure was achieved only in two-thirds of all cases (14 of 21, 67%) [1].

The reason for failure of DAIR in hip and knee PJI cases has been linked to resistance of bacteria, poor host and inability to remove modular components, which would then compromise the ability to perform meticulous debridement. Most surgeons will agree that the aforementioned factors are important ones influencing the outcome of DAIR. They will also posit that one of the most important metrics governing the success of DAIR is the method used by the surgeon to perform the procedure. Meticulous debridement and the use of copious antiseptic solutions are all believed to be an important part of bioburden reduction, which in turn affects the outcome of this procedure [4–6]. When DAIR is attempted, available literature infrequently gives in-depth insight into the surgical details – approach, volume and type of irrigation solution or, perhaps most importantly, the frequency of poly exchange versus retention.

Practically, the anterior approach is most commonly described [1–3] and poly-exchange frequently endorsed [3,4]. The duration of concomitant antibiotic prescription is most commonly six weeks of therapy (most commonly intravenous); however not all routes of administration or duration is conveyed in the literature reviewed [1–4,6]. The use of vacuum-assisted devices is not reported in the treatment of TAA infections, rather in the promotion of wound healing and the prevention of infection after primary elective arthroplasty [7,8].

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TABLE 1. Investigation of 34 cases of TAA infection

Author	Number of TAA Infections	Number of Attempted DAIR	Remission
Kessler et al. [1]	34	21	14/21 (67%)
Ferrao et al. [2]	6	0	6/6 (100%)
Myerson et al. [3]	19	4	All DAIR patients developed later infection and failed
Patton et al. [4]	29	5	Unknown for DAIR

TAA, total ankle arthroplasty; DAIR, debridement, antibiotics and implant retention

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QUESTION 7: What are the indications for one-stage versus two-stage exchange arthroplasty in management of the infected total ankle arthroplasty (TAA)?

RECOMMENDATION: Two-stage exchange arthroplasty is recommended in the majority of cases following infected TAA. One-stage arthroplasty is only indicated in a limited patient population with acute infection, preoperatively identified low-virulence organisms and low-risk patient factors.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 92%, Disagree: 8%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

The management of the infected arthroplasty remains a challenging and controversial topic in relation to any joint [1–5]. Reported rates of infection following TAA requiring re-operation (surgical irrigation and debridement (I&D), component removal and exchange, or revision) range from 0 to 8.6% [6–11]. Special consideration must be taken into account in the management of the infected total ankle given the tenuous soft tissue coverage, frequent history of multiple preceding operations, and, relative to hip and knee arthroplasty, a more recent arthroplasty design and more limited experience [12]. Currently, two-stage revision exchange arthroplasty surgery is the most popular surgical option for the management of periprosthetic joint infection (PJI) in North America and worldwide. However, it may result in significant bone loss, patient morbidity and prolonged disability, leading to a more challenging reconstruction and ultimately prolonged recovery, poorer patient-reported clinical functional outcomes, higher rates and risk of subsequent infection and potential failure of salvage operations leading to amputation.

Surgical treatment goals of the infected TAA are to eradicate the infection, obtain mechanical stability and soft-tissue coverage, alleviate pain and maximize clinical function. Historic treatment strategies have included antibiotics with hardware retention, aggressive debridement with or without polyethylene exchange and removal of hardware and exchange or arthrodesis in one or two stages with an antibiotic-impregnated cement spacer.

Extreme care should be taken when considering appropriate management of the infected TAA. Kessler et al. published the largest study to date evaluating 34 patients following revision TAA for infection [10]. An infection-free outcome with satisfactory function of the ankle was obtained in only 23 patients (67.6%). One-stage revisions with retention of one or both components resulted in 33.3% (7/21) failure with persistent infection, whereas two-stage revision with explantation of all components results in 10% (1/10) failure. Myerson et al. retrospectively evaluated 19 revision cases, and only 3 of the 19 patients underwent successful revision with replacement (15.7%), 6 with arthrodesis (31.6%), 7 with a permanent antibiotic spacer (36.8%) and 3 patients required a transtibial amputation (15.7%) [11]. Although prosthesis salvage was attempted in three early postoperative and one acute hematogenous cases, all revision cases ultimately required subsequent removal of the prosthesis. Whereas Myerson et al. reported that no patient was successfully treated with retention of the hardware, Patton reported conflicting results with four of four patients (100%) successfully treated with retention of hardware and irrigation and debridement (two with and two without exchange of polyethylene liner) for heterogeneous presentations (one acute presentations with cellulitis, one acute presentation with dehiscence, one late chronic, and one remote hematogenous) [12]. However, the majority of the patients in this study were treated with two-stage revision arthroplasty or amputation with retention of arthroplasty only achieved in 19 (65%) cases of infection (n = 29). Given the currently available literature, there are conflicting data for the utility of surgical I&D with retention of hardware. Future studies are necessary to evaluate the feasibility of surgical I&D of PJI in TAA.

To date, there is no level I evidence that provides indications or contraindications for a one-stage exchange arthroplasty in TAA. Furthermore, there are no randomized controlled trials that provide absolute indications or contraindications for two-stage exchange arthroplasty in hip and knee arthroplasty [13–16]. Care must be taken to determine the need for implant removal given that the reported success of treating the infected TAA with retention of one or both implants ranges from 0 to 100% [7,11,12]. Given the variability in the reported rates of success in eradicating infection, morbidity and mortality among observed patient populations and variable time periods prior to reimplantation, direct comparisons with one-stage exchange arthroplasty are difficult due to a patient selection bias in the current literature [15–18]. Although no literature is available with respect to TAA, a recent systematic review of the knee arthroplasty literature by Romano et al. demonstrated that a two-stage exchange provides, on average, a better outcome with respect to the control of infection in the knee [19]. The same group recently presented similar but less notable findings for the hip [20]. It is not clear how these findings would translate to the ankle, and future studies are necessary to better understand the potential for infection control and functional outcome with one- versus two-stage revision arthroplasty.

There are, however, circumstances that necessitate the removal of implants. Systemic infection necessitates timely administration of appropriate antibiotics and prompts removal of implants with thorough debridement of the soft tissues and bone in order to address the potential life-threatening sequelae of PJI. The immunocompromised patient or the presence of medical comorbidities, including metastatic disease, advanced cardiac disease and renal and/or liver dysfunction, have been shown to impact the rate of success for infection eradication and certainly influence morbidity and mortality [7,10]. It is unknown if the presence of these comorbidities constitutes a contraindication for one-stage exchange arthroplasty in TAA [14–16,18,21,22].

Since 1999, when Costerton first attributed the persistence of certain chronic infections to the presence of biofilm, the majority of implant-related infections in orthopaedics are believed to be secondary to biofilm-related infections [23]. These infections are associated with glycocalyx polysaccharide biofilms that pose unique challenges including frequently being recalcitrant to antibiotic treatment and may be culture-negative with ineffective clearance from the host [24,25]. Failure to identify the offending organism and/or culture-negative PJI is a relative contraindication to one-stage exchange arthroplasty [13,16,26,27]. Given the risk of biofilm-related

TABLE 1. Indications for one- versus two-stage exchange for infected TAA

Treatment Type	Indications
One-stage Exchange Arthroplasty	No sinus tract or exposed hardware Healthy patient and soft tissue No prolonged antibiotic use No significant bone loss requiring bone graft Low-virulence Organism with good antibiotic sensitivity
Two-stage Exchange Arthroplasty	**Sepsis.** Patients with systemic manifestations of infection **No Cultured Organism.** High suspicion for infection but no organism has been identified **Antibiotic-resistant Organism.** Preoperative cultures identifying difficult to treat and antibiotic-resistant organisms **High-risk Patient Factors.** a. Presence of a sinus tract or exposed hardware b. Immunocompromised c. Inadequate and non-viable soft tissue coverage d. Need to utilize higher order reconstructive techniques (bone graft, augmentation, soft-tissue flaps)

TAA, total ankle arthroplasty

infections, several authors advocate that reimplantation of a prosthesis should be delayed until adequate resuscitation and eradication of the offending organism have been confirmed [13–16,21,26–31].

The presence of compromised soft tissues (e.g., sinus tract, exposed hardware, etc.) that may limit adequate implant coverage is another indication for two-stage exchange arthroplasty. Sinus tracts frequently present with indurated, poorly elastic surrounding tissue near and around the ankle that limits the potential for adequate primary closure. In addition, the presence of a sinus tract may contaminate preoperative cultures and preclude the prerequisite for the identification of the offending organism [4,13,16,26,27]. Tissue expanders, musculocutaneous flaps and possible repeat debridements may all be indicated, necessitating further time between initial resection and reimplantation [14–16,22]. If soft tissue coverage cannot be obtained at index revision of a one-stage exchange arthroplasty, a two-stage surgery should be considered [13–15].

If the decision is made to pursue two-stage arthroplasty, there is no definitive evidence in the literature concerning the optimal timing between the two stages. However, there should be ample time to allow administration of a complete full course of antibiotics, eradication of the offending organism supported by a decrease in inflammatory markers (C-reactive protein [CRP]/erythrocyte sedimentation rate [ESR]), and adequate soft tissue preparation. Although no literature exists demonstrating the optimal timing of replantation in TAA, there is evidence that replantation prior to completing a complete six-week course of antibiotics may result in increased positive cultures at the time of surgery in the hip and knee [14,16]. In the United States, the most common practice is to complete a course of six weeks of intravenous or oral antibiotics followed by a cessation of antibiotics for two to eight weeks prior to reimplantation [16,32,33]. In addition, in the adult hip arthroplasty literature, there is evidence that delaying replantation beyond six months impairs functional improvement compared to patients who underwent two-stage exchange within six months of resection and reimplantation [34]. Although we recommend trending the ESR and CRP, the need for serologic evaluation prior to reimplantation is unclear. Although ESR and CRP alone are poorly diagnostic of persistent PJI with no optimal cutoff values, changes in inflammatory marker values from the time of resection may demonstrate improved pathogen control and decreased overall biologic burden [15,35–37]. There is currently no literature with respect to TAA to guide decision-making on the optimal timing between exchanges, nor serologic cutoff values.

All patients, regardless of nonoperative or operative management, should be critically evaluated clinically and every effort to minimize the risk of wound breakdown should be pursued, including optimization of diabetes, reduction of inflammatory conditions, the absence of tobacco use and optimal nutrition. Soft tissue defects may require flap coverage. We recommend revision to ankle arthroplasty after clearance of infection.

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QUESTION 8: What metrics can be used to determine the optimal timing of reimplantation in patients who have undergone resection arthroplasty as part of a two-stage exchange for infected total ankle arthroplasty (TAA)?

RECOMMENDATION: There is no conclusive data regarding what metrics can be used in order to determine the optimal timing of reimplantation for an infected TAA. We recommend that reimplantation is performed when there are clinical signs of resolution of infection (well-healed wound, lack of erythema, etc.), and the serological markers have substantially declined (> 40%) from baseline (measured at the time of diagnosis of infection).

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infected TAA is a serious complication that is thought to occur in as many as 5% of patients [1,2]. Management of infected TAA often requires surgical intervention that includes removal of the prosthesis, local and systemic antibiotic treatment, and subsequent reimplantation in a select group of patients. One of the most challenging questions pertains to optimal timing of reimplantation. There is little in the literature regarding the optimal treatment of an infected TAA. Most of the available literature has limitations including low numbers of patients, short duration of follow-up and so on [1–5].

There are a number of publications related to patients with infected TAA who underwent two-stage exchange arthroplasty. Patton et al. reported on 29 of 966 (3.2%) cases of infected TAA [3]. Among the infected TAA, 13 patients underwent two-stage exchange arthroplasty and antibiotic spacer placement. While infection type and operative cultures were listed, no specific recommendations on timing of reimplantation were made. Similarly, Lee et al. omitted data regarding timing of reimplantation but reported one case of deep infection, out of 50 TAAs (2%) that required implant removal, antibiotic-impregnated spacer placement, and later revision TAA [4].

Thoroughly outlining the timeline, Young et al. detailed a case report of a two-stage TAA revision [5]. Irrigation and debridement (cefazolin 1 gm diluted in 1L 0.9% saline) and antibiotic cement

spacer (80 gm of polymethylmethacrylate impregnated with 2 gm gentamicin) placement was implemented. The blood cultures and intraoperative bone and tissue cultures in the latter infected case isolated *Streptococcus mitis*. As a result, a six-week course of antibiotics with penicillin G was administered. Three months after infection had resolved, the patient had a revision TAA. As demonstrated, the limited TAA infection literature warrants that a treating orthopaedic surgeon applies the basic treatment principles derived from infections of knee and hip arthroplasties [6].

The ultimate decision regarding surgical management of patients with infected TAA in general, and reimplantation of those who have undergone a prior resection in particular, lies with the orthopaedic surgeon with appropriate consultation of other disciplines such as infectious disease specialists, plastic surgeons and so on. A two-stage exchange strategy is commonly indicated in patients who have a chronic infection and are not candidates for a one-stage exchange arthroplasty. Protocols for management of a patient with infected TAA are extrapolated from the available literature for infected hip and knee arthroplasties. Patients undergoing resection arthroplasty typically receive four to six weeks of intravenous or highly bioavailable oral antimicrobial therapy between stages [7,8].

The timing to reimplant usually relies on signs of clinical resolution of infection, such as healing of the wound, absence of erythema and so on, as well as a decline in serological markers of inflammation, namely erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [9]. To determine infection resolution and predict the presence of infection in patients awaiting reimplantation, numerous serological markers have been evaluated in the past, including interleukin 6 (IL-6) and others [10]. The most widely used serological tests for the diagnosis of periprosthetic joint infection (PJI) are the assessment of ESR and CRP level. A recent publication also suggested the use of serum D-dimer combined with ESR and CRP in order to increase sensitivity and specificity [11].

In data published about hip and knee surgery, time from resection arthroplasty to reimplantation varies significantly from two weeks to several months. In earlier cohort studies, early reimplantation within three weeks after resection resulted in a higher failure rate [12,13]. Some groups have reported satisfactory outcomes when reimplantation occurs two to six weeks after resection while systemic antimicrobials are still being administered in situations when the infection is not due to MRSA, enterococci or any multidrug-resistant gram-negative organisms [14]. Delayed reimplantation after four to six weeks of intravenous antimicrobial therapy and an antibiotic-free period of two to eight weeks has been highly successful and chosen as the "standard" currently [7,15–17]. Recently, synovial fluid biomarkers have been shown to be useful in reaching or refuting the diagnosis of PJI. The combined measurement of synovial fluid alpha-defensin and CRP for the diagnosis of PJI demonstrated a sensitivity of 97% and a specificity of 100% [11,18]. Not only is obtaining synovial fluid invasive and painful to patients, but also there are not infrequent occasions when either an inadequate amount of fluid is available to perform all tests, or, worse, no fluid is retrieved from the joint [11].

Obtaining a pre-revision ESR and CRP is recommended to assess the success of treatment prior to reimplantation [19]. However, as some groups have reported, an elevated CRP level and ESR may not be accurate in predicting persistent infection post-resection, therefore the need for subsequent debridement should be interpreted in the context of the entire clinical picture when deciding on the appropriate timing for reimplantation [20–22].

In the absence of concrete data, and borrowing from the hip and knee infection literature, we recommend that reimplantation in patients with infected TAA be performed when appropriate antibiotic treatment is completed, clinical signs for resolution of infection are present (healed wound, absent erythema and so on) and the level of inflammatory markers of acute inflammation (ESR, CRP and possibly D-dimer) have declined substantially (> 40%) from their baseline. Further research regarding this issue is desperately is needed.

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QUESTION 9: What are the predictors of treatment failure in patients who have undergone two-stage exchange for infected total ankle arthroplasty (TAA)?

RECOMMENDATION: Predictors for treatment failure in patients undergoing two-stage exchange for infected TAA include compromised soft tissues (e.g., sinus tract, exposed hardware, etc.), significant bone involvement/osteomyelitis and insufficient timing of antibiotic course before reimplantation.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The optimal management of patients with infected TAA is not well-known due to a limited number of studies [1–5]. While comparisons and deductions can be made from the knee and hip periprosthetic joint infection (PJI) literature on two-stage exchange, the management of infected TAA can differ from hip and knee arthroplasty because of the precarious soft tissue coverage around the ankle, the common history of multiple preceding operations in patients, and arthroplasty design updates coupled with limited surgical experience [3]. Two-stage exchange is a well-accepted surgical management approach for PJI.

There is limited detail in the TAA literature on two-stage exchange failure. A study by Patton et al. reported on 12 cases of two-stage revision for infected TAA but offered no details of the cases that failed [3]. Another study by Kessler et al. reported on 34 patients undergoing surgical management for infected TAA [6]. Of the patients treated for infected TAA, 10% (1/10) of two-stage exchanges resulted in failure. This two-stage failure is not described in detail. However, in the described cohort, the presence of compromised soft-tissue significantly increased the rate of failure after revision.

Another problem with the soft tissues surrounding the ankle is the presence of a sinus tract. Not only do sinus tracts often have indurated soft tissue around the ankle, but they also have the potential to limit preoperative cultures and organism identification, which in itself may predispose the patient to a future failure [7–11]. Furthermore, certain comorbidities such as metastatic disease, renal and/or liver dysfunction, and advanced cardiac disease are indicated to influence the rate of PJI [6,7], but these comorbidities may not necessarily be tied to treatment failure after two-stage exchange arthroplasty.

In North America patients undergoing two-stage exchange arthroplasty for the treatment of PJI are often subjected to six weeks of an antibiotic course. Based on data from hip and knee PJI, inadequate administration of antibiotics has been linked to the presence of positive cultures during reimplantation that, in turn, increase the risk of failure after reimplantation [8,13]. While inadequate antibiotic therapy has been linked with subsequent failure, the exact duration of antibiotic treatment, the benefit of intravenous (IV)-to-oral (PO) antibiotics, and the timing of IV-to-PO switch has not been determined. Recent PJI literature suggests that a short IV antibiotic period lasting at least five to seven days followed by pathogen-specific PO therapy may be a viable option for treatment of patients with PJI [14,15].

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QUESTION 10: How should postoperative cellulitis be treated in patients with total ankle arthroplasty (TAA) in place?

RECOMMENDATION: In the absence of evidence, we recommend that (1) patients with TAA in place who develop postoperative cellulitis be evaluated thoroughly to rule out periprosthetic joint infection of the ankle, and (2) that isolated cellulitis may be treated with antibiotics, elevation and close monitoring. Aspiration can be considered in certain cases, with the potential risk of introducing deep space infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 92%, Disagree: 0%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

Treatment of postoperative cellulitis in patients with TAA is not well-defined. Schipper et al. suggested a compression wrap protocol over a circumferential fiberglass cast significantly reduces the incidence of wound complications [1]. While the authors demonstrated an overall reduction of wound complications, the differing postoperative immobilization protocols did not result in a significant difference in the proportion of wounds in patients with cellulitis requiring antibiotics (oral or intravenous) (22% vs. 16.7%, p = .60).

To our knowledge, there is no other TAA literature reporting on cellulitis. Brook and Frazier reported on 259 patients with culture-positive cellulitis [2]. Based upon their report in which 63 of 259 (24%) cellulitis cases were located on the leg, the authors concluded that the polymicrobial nature of cellulitis warrants the prescription of broad-spectrum antibiotics.

Meanwhile, in the total hip arthroplasty (THA) population, Rodriguez et al. reported on the use of intravenous and oral antibiotics in 16 patients with incisional cellulitis [3]. They assessed the erythematous eruption by hematological investigations, radiography, radionuclide scanning and blood culture, as well as aspiration from the area and skin biopsy. Following assessment, the best antibiotic course was determined. For two to six days until the erythema resolved, the following antibiotics were given to patients: 11 were given cephalexin, one vancomycin, one ampicillin and gentamicin and one cefuroxime. Following this antibiotic course, cephalexin, ciprofloxacin or amoxicillin were administered orally for two to six weeks. One patient received only oral ciprofloxacin, with resolution of the erythema occurring within 24 hours. Rodriquez et al. thus concluded that treatment with antibiotics for a minimum of two weeks led to resolution of symptoms and allowed for nonoperative management of the cellulitis.

In a separate case report on a patient undergoing THA, Perlick et al. argued that most cellulitis is caused by *Streptococcus hemolyticus* or *Staphylococcus aureus* [4]. The authors were successful in treating the surgical site cellulitis with the following protocol: dicloxacillin 2 gm × 3 or clindamycin 600 mg × 3 daily. This finding should also be considered when determining an appropriate treatment regimen for patients with post-arthroplasty cellulitis.

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Authors: Jonathan Kaplan, Steven Raikin

QUESTION 11: Does deep chronic infection after total ankle arthroplasty (TAA) require implant removal?

RECOMMENDATION: Yes. Deep chronic infection after TAA requires implant removal unless otherwise contraindicated.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

While there is substantial evidence in the total hip arthroplasty (THA) and total knee arthroplasty (TKA) literature regarding one- and two-stage revision for infected total joint arthroplasty (TJA), there are very limited studies assessing deep chronic infection in primary TAA and TAA revisions. The majority of recommendations for the evaluation and treatment of the infected ankle arthroplasty in the current literature are based on those recommendations of THA or TKA [1–3]. Hsu et al. reported on the evaluation and management of the painful

TAA. In cases of deep infection in the early period (< 4 weeks), the authors recommended irrigation and drainage (I&D) with polyethylene exchange and intravenous (IV) antibiotics. In infection cases occurring > 4 weeks from the time of initial implantation, a two-stage surgery was required. However, it should be noted that this determination was again based on the THA and TKA literature rather than studies specifically assessing infected TAA [4].

Myerson et al. performed a retrospective review on the management of infection following total ankle replacement [5]. Over a 10-year period, the authors performed 613 total ankle replacements with a deep infection rate of 2.4%. There were 15 late/chronic infections, three early infections and one acute hematogenous infection. In the three early and one acute hematogenous infections, the authors attempted I&D, polyethylene exchange and retention of the components in conjunction with a course of IV antibiotics. Unfortunately, all four patients developed recurrent infection requiring repeat I&D and complete prosthesis removal with antibiotic spacer placement. In the chronic/late infections cohort, they performed a two-stage revision with initial I&D, complete explantation, cement spacer application and IV antibiotics. Of these 15 chronic infections, infection recurrence occurred in three patients, requiring additional interventions. Additionally, from the same institution, Ferrao et al. reported on the definitive treatment of infected total ankle replacements using an antibiotic cement spacer in cases in which revision would not be amenable [6].

In a related study, Patton et al. reported on their experience with infected TAA [3]. Out of 966 patients undergoing TAA, there were a total of 29 infections, accounting for an overall infection rate of 3.2%. They classified these based on acute postoperative complications including cellulitis or wound dehiscence, late chronic infection or remote hematogenous. There were 11 cases of acute postoperative wound dehiscence, three cases of acute postoperative cellulitis, eight cases of remote hematogenous infection and seven cases of late chronic infection. Of the 14 cases in the acute stage (cellulitis and wound dehiscence), one was treated with I&D, polyethylene exchange and antibiotic treatment, three were treated with I&D and antibiotics, four were treated with two-stage exchange revision, one was treated with a one-stage revision, one was treated with permanent antibiotic spacer placement and four were treated with amputation. Of the seven late chronic infections, five were treated with two-stage procedures, one was treated with amputation and one was treated with polyethylene exchange. In the eight cases of remote hematogenous infection, one was treated with amputation, six were treated with two-stage procedures and one was treated with I&D. While the authors report a variety of procedures for each of these presentations based on timing, it should be noted that they defined infection in the early postoperative phase as cellulitis and wound dehiscence rather than an objective diagnosis of deep infection. Additionally, while there were cases of single-stage procedures, these were quite low numbers compared to two-stage procedures or even amputation.

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3.2. TREATMENT: NON-TOTAL ANKLE ARTHROPLASTY-SPECIFIC

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QUESTION 1: What is the treatment "algorithm" for infection after ankle or hindfoot arthrodesis?

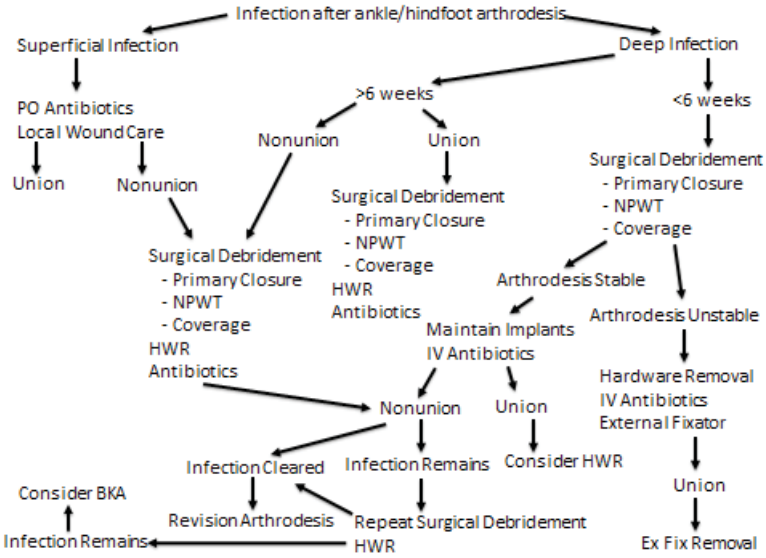
RECOMMENDATION: There is no universal algorithm for addressing the infected ankle or subtalar arthrodesis. A potential algorithm created by consensus is:

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infection after ankle or hindfoot arthrodesis always results in a protracted recovery. Recovery from this complication may include multiple surgeries, escalating cost and may result in a painful and poorly-functioning limb. Patients with suspicion of infection following ankle or hindfoot arthrodesis should be evaluated for deep versus superficial infection as well as appropriate host and surgical factors to determine the most appropriate treatment. Superficial infections may be treated with irrigation and debridement (I&D), local wound care and pathogen-specific antibiotics. Deep infections involving the internal hardware should prompt hardware removal. Additional components of treatment may include some combination of placement of antibiotic beads or spacers, stabilization with external fixation to temporarily stabilize or achieve definitive arthrodesis [1] and delayed revision arthrodesis with internal fixa-



HWR, hardware removal; NPWT, negative-pressure wound therapy

tion following eradication of infection. The patient's nutritional and vascular status should be optimized. If soft tissue coverage is necessary, a multidisciplinary approach is necessary to determine the viability of the extremity. To achieve fusion, a radical debridement, stable fixation and minimal compromise of the marginal blood supply are necessary.

All patients should be critically evaluated in a multidisciplinary approach to optimize the patient's health and psychological status. Every effort to minimize the risk of wound breakdown should be pursued including optimization of diabetes, reduction of inflammatory conditions, the absence of tobacco use and optimal nutrition. The impact of prolonged impaired mobilization, possible unemployment and social isolation should not be neglected and may compromise patient adherence for further surgery and postoperative regimens, as well as diminish functional outcomes. We recommend an appropriate evaluation of the patient host and arthrodesis surgical factors in patients with infection following tibiotalar or subtalar arthrodesis.

Infection following ankle or hindfoot arthrodesis may significantly delay bony consolidation. Frey et al. reported as high as 60% nonunion rate following ankle fusion complicated by infection [2]. In order to address the infected ankle or hindfoot fusion, several algorithms have been proposed [1,3]. Any patient in which bony fusion is uncertain should be evaluated by computerized tomography (CT) to assess the arthrodesis. Debridement followed by arthrodesis remains the salvage procedure of choice for the infected ankle and subtalar joints, and has proven to be an effective means for limb salvage and maximizing patient functional outcome [1,3–5]. Härle reported the results of a two-stage procedure with the treatment of infection first by implant removal, thorough debridement and implantation of Septopal® (Gentamicin-PMMA chains) beads, followed by secondary internal stabilization with an antibiotic-releasing bone plate. Although 3 of the 42 patients (7%) ultimately required an amputation, infection was cured long-term in 36 (84%), and 39 (93%) achieved stable bony fusion [3]. Paley et al. recommended removal of all internal hardware and sharp debridement of all necrotic and infected tissue followed by external fixation and reported 100% union [1]. Baumhauer et al. reviewed the literature on arthrodesis of an infected ankle and subtalar joint but did not suggest an algorithm for treatment of infection after ankle or subtalar joint, arthrodesis [6].

Host Factors

Host factors must be optimized prior to undergoing reoperation. Malnutrition, diabetes and nicotine cessation should be advocated. Preoperative malnutrition has been associated with delayed wound healing [7], longer length of stay and anesthesia/surgical times [8] and failure of treatment of persistently draining wounds inevitably leading to deep infection [9]. The measures of malnutrition have varied and may be defined by a variety of methods including serological laboratory values (e.g., transferrin, total lymphocyte count, serum albumin and prealbumin), anthropometric measurements, and standardized scoring tools [10]. The most common definitions of malnutrition are total lymphocyte count (TLC < 1500/cc) and serum albumin (< 3.5 gm/dL) [9,11,12]. Frey et al. reported that patients with major medical problems including renal failure, significant smoking history, diabetes and alcohol abuse demonstrate an 85% nonunion rate following attempted ankle fusion [2]. Jaberi et al. reported successful salvage of patients undergoing hip and knee arthroplasty in only 5% of malnourished patients treated with I&D [9].

Diabetes

Perioperatively elevated blood glucose levels and complicated diabetes mellitus prior to elective surgery predispose patients to postoperative soft tissue and bone healing complications [13–18]. The current guidelines, as published by the American Diabetes Association, recommend that surgery should be avoided if possible for those patients with hemoglobin A1c (HbA1c) greater than 7% [19]. In an effort to validate the recommendation, Jupiter et al. assessed the relationship between the HbA1c levels and the rate of postoperative infection [20]. Their results indicated that infection rates increase steadily as the HbA1c increases toward 7.3%, increase rapidly at an HbA1c of 7.3% to 9.8%, and then level off. Several studies demonstrate an increased risk of infection following arthroplasty in patients

with HbA1c greater than 6.5% [20–22]. Although it is unclear in foot and ankle literature whether any specific HbA1c should serve as a contraindication for revision fusion, multiple studies have demonstrated that diabetic neuropathic arthropathy contributes to high complication and failure rates. Ankle and subtalar arthrodesis should thus be considered with caution in the diabetic patient [23].

Tobacco

All efforts should be made to eliminate exposure to nicotine and tobacco products. Studies have demonstrated that patients who smoke tobacco are at three times greater risk of hindfoot nonunion [24]. Fragomen et al. reported a 54% nonunion rate in tobacco users who smoke undergoing primary arthrodesis [25]. Patients who undergo revision are certainly at higher risk of both osseous nonunion and soft tissue complications following revision hindfoot nonunion. Although the literature is unclear, we recommend waiting at least six weeks following smoking cessation in order to reduce the risk of pulmonary complications associated with rebound mucosal secretions and increased perioperative complications associated with smoking cessation in the perioperative period. In addition, we recommend confirming cessation via testing for nicotine and its primary breakdown product (metabolite) cotinine in the blood, urine, saliva or hair. Cotinine is widely used when compared to other diagnostic tools because of its higher sensitivity, specificity and long half-life, as well as the fact that it is the best indicator for distinguishing the tobacco users from non-users. We prefer urine biomarker testing over serum given its high sensitivity compared to blood cotinine and minimally invasive collection [26,27]. We recommend a urinary cutoff of greater than or equal to 2.47 ng/ml to detect the highest sensitivity and specificity of 100% for smoking [28].

SURGICAL PROCEDURES

Irrigation and Debridement

Isolated surgical I&D should be reserved for soft tissue infections that are not in direct communication with hardware. Given the risk of persistent chronic infection following infected ankle or hindfoot arthrodesis, we do not recommend isolated I&D of the deeply infected arthrodesis. If there is any uncertainty concerning whether the retained hardware is in communication with infected tissue, the hardware should be removed given the high failure rate associated with retained hardware [1,3–5].

Soft Tissue Coverage

The overlying soft tissue must be evaluated to determine whether adequate soft tissue coverage is possible; sinus tracts may be excised and hardware remains exposed. Multidisciplinary assistance from plastic surgery may be necessary if primary or delayed primary is not possible and if the surgical site necessitates a local or free flap for closure. Commonly utilized flaps for the hindfoot may include reverse sural flap or free flap (e.g., anterolateral thigh via the circumflex femoral pedicle, superficial circumflex iliac artery perforator and thoracodorsal artery perforator flaps) [29].

Bone Stock

Viable bone must be evaluated to determine remaining available bone for reconstruction and possible salvage arthrodesis [30]. There are limited case reports of salvage tibiotalocalcaneal (TTC) arthrodesis with a custom titanium alloy truss and retrograde intramedullary nail for hindfoot infection with bone loss [31]. We were unable to identify any clear literature on the most appropriate management of the infected ankle and subtalar arthrodesis with significant osteolysis, subsidence or bone loss following excision of bone with osteomyelitis.

Explantation of Hardware

In 1999, Costerton attributed the persistence of certain chronic infections to the presence of biofilm, and since then the majority of implant-related infections in orthopaedics are believed to be biofilm-related infections associated with glycocalyx polysaccharide biofilms that are often recalcitrant to antibiotic treatment and may be culture-negative with ineffective clearance from the host [32,33]. Given the risk of biofilm-related infections, reimplantation of a prosthesis should be delayed until adequate resuscitation and eradication of the offending organism has been completed [34–44]. However, Paley et al. supported using external fixation following explantation of hardware in the infected failed hindfoot fusion [1].

FIXATION TECHNIQUES

Internal Osteosynthesis

Several techniques have been reported for utilizing plate fixation for revision ankle arthrodeses [45–49]. However, successful internal fixation following infection has only been described in the setting of the septic ankle. Klouche et al. reported the outcomes of 20 patients who underwent tibiotalar arthrodesis in the presence of sepsis with internal osteosynthesis resulting in a fusion rate of 89.5% and clearance in 85.0% of cases [50]. Richter et al. reported solid ankle or hindfoot arthrodesis following infection in 39 of 45 patients (87%) utilizing hybrid fixation with both internal (compression screws and an anterior plate) and external fixation [51].

External Fixator

TTC arthrodesis using the Ilizarov technique is a viable alternative to amputation in patients with infected nonunions or large bone loss of the tibia or talus precluding internal fixation with reported fusion rates as high as 77 to 93% [5,52–54]. Saltzman reported on eight patients with diffuse ankle osteomyelitis who were treated with resection of the infected bone and application of a compressive circular external fixator. Six weeks of intravenous antibiotics were administered and wound vacuum devices were applied over open wounds. Sepsis was eradicated in all [55]. It should be noted that these patients had the diagnosis of osteomyelitis, but not specifically an infected ankle or hindfoot arthrodesis. Similarly, Raikin recommended I&D, a six-week course of intravenous antibiotics, removal of internal hardware and stabilization of the arthrodesis with an external fixator. A vacuum device or plastic surgery coverage was recommended for an open wound [56]. For failed ankle arthrodeses, Hawkins et al. reported on 21 cases which were salvaged with the Ilizarov technique. Of the patients 80% achieved fusion and resolved infection [57]. Although external fixation is typically indicated for patients with active or previous infection, union rates and outcome measures of external fixation are inferior to internal fixation [58].

Intramedullary Fixation

Techniques utilizing an antibiotic-impregnated intramedullary polymethyl methacrylate (PMMA) nail or antibiotic-coated intramedullary nail have been described [59–61]. To achieve successful fusion in the setting of infection, it is important to not only remove any hardware with potential formation of glycocalyx polysaccharide biofilm but also to avoid introducing new foreign bodies at the site of infection, and, therefore, external fixation is often

considered the gold standard. However, antibiotic-coated intramedullary nails may also be considered if acute shortening and bone contact may be achieved [61,62]. The current literature supporting antibiotic-coated nails for the treatment of infected ankle nonunions and infected distal tibial fractures to achieve fusion, improve patient functional outcomes and successfully eradicate infection are encouraging. However, these studies are limited to small case series. Future studies are necessary to better understand the potential for union, functional outcome and infection control utilizing intramedullary antibiotic-coated nails following infected ankle or hindfoot arthrodesis.

USE OF ANTIBIOTIC-IMPREGNATED ADJUNCT

All patients with infection following ankle or hindfoot arthrodesis procedures should be administered oral, intravenous and/or local antibiotics. Consulting your local infectious disease physician may be warranted to better assess local antibiotic nomograms and assist in recommendations. Antibiotic-loaded PMMA has demonstrated to be successful in treating osteomyelitis and is commonly used for antibiotic release to the site of infection but displays variable elution kinetics and represents a potential nidus for infection, therefore requiring surgical removal once antibiotics have eluted [63,64]. Definitive treatment with an antibiotic spacer can be considered and has been reported. Ferrao et al. reported on the use of a cement spacer after deep ankle infection. Three patients underwent an ankle arthrodesis, and the remaining six underwent TAA. Most retained their cement spacers, and those who did were ambulatory with little discomfort [65]. Alternatively, antibiotic-loaded calcium sulfate beads have the benefit of serving as an osteoconductive material with time-dependent antibiotic delivery, but have been criticized for the massive amount of drainage secondary to hydrolysis-dependent antibiotic delivery [66]. The concept of local antibiotic deposition is particularly critical in poorly-perfused limbs. The use of antibiotics in bone cement or calcium sulfate biocomposites offers several advantages, including the ability to achieve high local levels of antibiotic [67], low systemic toxicity [68,69] and minimal local tissue toxicity [70,71]. The high local antibiotic levels achieved also allows for a decreased need for systemic antibiotic usage, which is especially useful in patients who are intolerant to prolonged systemic antibiotics [64].

Amputation

Surgeons making a choice between arthrodesis and amputation need to consider the clinical situation of the individual and patient preference. Amputation of the failed infected hindfoot arthrodesis may be appropriate in select cases involving non-ambulatory patients, infection resistant to aggressive debridement and antibiotics, severe bone loss or extensive osteomyelitis that precludes arthrodesis, inadequate soft tissue coverage or peripheral vascular or neurovascular injury. Severe immunocompromising states inhibit both infection eradication and wound healing and may be prohibitive for revision or may necessitate amputation. Active intravenous drug abuse may be a contraindication to salvage of the failed infected hindfoot fusion and may also indicate the need for an amputation. Contraindications to revision may apply to non-ambulatory patients or those with extensive medical comorbidity that precludes multiple surgeries.

Biophysical Augmentation

Biological supplementation has been studied in at-risk ankle unions as well as nonunions. Given the reported high rates of nonunion and malunion in primary hindfoot and ankle unions [72], it is common practice to use some biological adjunct therapy to improve the chance of fusion including bone marrow aspirate, platelet-rich plasma (PRP), recombinant human bone morphogenetic protein-2 (rhBMP-2), cancellous bone allograft, recombinant human platelet-derived growth factor (rhPDGF-BB) in combination with a ß-TCP-collagen matrix, cryopreserved cellular bone allograft, map3 cellular allogeneic bone graft and cryopreserved amniotic membrane-umbilical cord allograft [73–77]. No study has specifically evaluated the efficacy and safety of biological adjuncts in the setting of the infected ankle and hindfoot nonunion.

Various external and internal osteobiologic devices have been shown to promote healing when used in complex ankle fusion. Three commercially distinct modalities have been investigated for bone stimulation, including pulsed electromagnetic field [77,78], internal direct current [79–82] and low-intensity pulsed ultrasound [83–85]. However, no study has specifically evaluated the impact of biophysical adjuncts following infected ankle or subtalar arthrodesis and further additional randomized controlled trials are necessary before justifying their utility.

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QUESTION 2: What is the optimal antibiotic (type, dose and route of administration) treatment for infections after foot/ankle fracture or fusion procedures?

RECOMMENDATION: The optimal antibiotic treatment after foot/ankle fractures or fusion should be determined based on the result of culture. In the absence of culture results, administered antibiotics should include coverage against common pathogens such as *Staphylococcus aureus*.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The commonality in the literature when addressing infection following traumatic foot/ankle procedures or fusions is to target antibiotic therapy to the specific pathogen [1–6]. This is achieved by taking intraoperative cultures, often preceded by preoperative joint aspiration. The majority of the literature suggests a six-week course of intravenous antibiotics; however, the range of recommended therapy is five days to three months [2,5,7].

The second method for delivery of antibiotics is by the incorporation of the antimicrobial agents into the cement spacer when surgical intervention is used [1,2,8]. Since conventional cultures used to identify the infecting organism are often obtained at the time of surgery, the offending pathogen is often not known preoperatively. In this situation, or when the culture results are negative, broad-spectrum antibiotics should be administered. Vancomycin is most commonly used, not infrequently in conjunction with tobramycin or gentamycin [1,5,9].

Methicillin-sensitive *Staphylococcus aureus* (MSSA) is the most common pathogen identified with post-traumatic/post-fusion foot and ankle infections [1,4,6,10,11]. The second most common infectious organism is *Staphylococcus epidermidis* [6,12]. Multi-drug resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), are also isolated in cultures with some regularity [6,11]. Diabetic patients have some increased risk of *Pseudomonas* infections as compared to non-diabetics [4]. Importantly, rare bacteria have been identified in case reports and polymicrobial infections have been regularly reported as well [5,13].

There is great heterogeneity in those patients being treated for post-traumatic/post-fusion infection, so it is difficult to interpret outcomes with regard to recurrent infection, ambulatory status/functionality and bony union [1,2]. Stability contributes to the resolution of infection and it has been proposed that antibiotic-coated retrograde nails can also provide local antibiotic delivery [14]. Even for those patients deemed inappropriate for a return to the operating room and for those treated definitively with an antibiotic-laden spacer, independent ambulation can be reliably achieved [3].

In conclusion, we recommend that the treatment of any foot and ankle infections following fracture or fusion procedures be based on the results of the culture, whenever available. In the absence of culture results, broad-spectrum antibiotics should be used.

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QUESTION 3: What is the treatment "algorithm" for infection after Achilles tendon repair/reconstruction?

RECOMMENDATION: The initial treatment of an infected Achilles tendon reconstruction should include thorough debridement of all infected tissues with the removal of retained sutures or foreign material. Cultures should be taken at the time of debridement and antibiotic administration should be dictated by the result of culture and continued until inflammatory markers and clinical symptoms normalize. If significant soft tissue defect in the overlying area remains, the choice of tendon reconstruction and/or transfer with soft tissue coverage should be left up to the discretion of the treating surgeon based on preference and expertise. Revision reconstruction should be delayed until the infection is cleared.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infection following Achilles tendon repair/reconstruction is a potentially catastrophic complication of a relatively common orthopaedic procedure. Wound complications following Achilles tendon repair occur in approximately 10% of cases [1], although the proportion of patients requiring secondary surgery or prolonged care has been reported to be substantially lower (2.44%) [2]. The loss of Achilles tendon tissue and soft tissue coverage secondary to infection leads to poor results and can be difficult to manage [3].

The optimal treatment of an infection following Achilles tendon repair/reconstruction consists of infection eradication, maintenance or restoration of ankle plantar flexion and soft tissue coverage. A literature search for the treatment of infection following Achilles tendon repair/reconstruction reveals a heterogeneous collection of expert opinions and case reports/series on how to accomplish these goals, with no definite consensus. While the literature generally agrees that the most important aspect of treatment revolves around an extensive debridement of the infected/necrotic tissue and antibiotic coverage, each author has their own opinion on how tendon and soft tissue defects should be addressed. These opinions range from extensive debridement with functional rehabilitation alone [4,5], to local tendon/tissue transfer [6–11], to free flaps [12–17]. Additional variations of treatment include single versus staged procedures [18,19], the utilization of cement spacers [18,19], tissue expanders [19] and negative pressure wound therapy [20,21].

Given the heterogeneity of the literature and the lack of any high level of evidence publications on the subject matter, we are unable to formulate a definitive consensus statement with regards to soft tissue coverage of the infected Achilles tendon following a prior repair/reconstruction. There is, however, evidence to suggest that thorough debridement of all infected tissue with the removal of retained suture or foreign material and antibiotic administration should be the initial step in the treatment of these patients. Cultures should also be taken at the time of debridement and antibiotic administration should be culture-driven and continued until inflammatory markers and clinical symptoms normalize. If significant defects remain in the Achilles tendon and overlying soft tissue following debridement, the choice of tendon reconstruction and/or transfer with soft tissue coverage should be left to the discretion of the treating surgeon based on preference and expertise.

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QUESTION 4: Should treatment of diabetic foot osteomyelitis be based on bone biopsies?

RECOMMENDATION: Yes. Bone biopsies play both a crucial diagnostic and interventional role in the management of diabetic foot infection. While bone biopsies are not required in every case of diabetic foot infection, their most important role is in guiding accurate antibiotic treatment, as they provide more accurate microbiological information than superficial soft tissue samples in patients with diabetic foot osteomyelitis.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Diabetic foot infections of the skin and soft tissue can lead to contiguous spread to underlying bone, resulting in osteomyelitis. Where a diabetic foot ulcer fails to heal with no other apparent reason or when exposure of bone is observed, osteomyelitis should be suspected. Plain radiography has demonstrated to have poor sensitivity in detecting osteomyelitis in the early stages [1].

Moreover, plain radiography and other imaging modalities do not identify pathogenic organisms, and, thus cannot guide antibiotic therapy. Despite the ease of obtaining superficial wound swab cultures, the cultured organisms are polymicrobial and do not correlate well with bone biopsy cultures and, therefore, should not be used to guide antibiotic therapies [2–6]. A single retrospective multicenter cohort study reported that the rate of infection resolution was significantly higher in the group for whom the choice of antibiotic regimen was based on bone culture versus those based on wound swab culture (82% vs. 50%, p = 0.02) [7].

Bone biopsies taken for microbiological and histopathological analysis are the gold standard for a definitive diagnosis of osteomyelitis [8–10]. A specimen can be obtained either transcutaneously through uninfected skin or as part of an operative procedure following debridement. Bone biopsies play both a crucial diagnostic as well as interventional role in the management of diabetic foot infection. While bone biopsies are not required in every case of diabetic foot infection, their most important role is in guiding accurate antibiotic treatment.

A positive microbiological result is where one or more pathogens from a reliably-obtained bone specimen is cultured [11]. It has shown to give a sensitivity of 92% and specificity of 60% in diagnosing diabetic foot osteomyelitis [12]. Reliable and accurate identification of the causative pathogens in diabetic foot infections is important, as prolonged antimicrobial therapy is tailored according to microbiological susceptibility profile. Most diabetic foot osteomyelitis cases are polymicrobial, with *Staphylococcus aureus* being the most commonly isolated pathogen (50% of cases). Other frequently isolated organisms include coagulase-negative staphylococci, *Enterobacteriaceae*, aerobic streptococci and *Pseudomonas aeruginosa* [8,13,14]. Contamination of contiguous wound colonizing flora and skin commensals may give a false positive result, whereas prior antibiotic therapy, patchy infectious involvement or inability to culture fastidious organisms may yield false-negative results [11].

Positive histological findings include aggregates of inflammatory cells (neutrophils, lymphocytes, histiocytes and plasma cells), erosion of trabecular bone, marrow changes (fat necrosis, edema, fibrosis and reactive bone formation) [11,15,16]. Other causes of inflammation may give false-positive histological results, whereas sampling errors can give a false-negative result. Histological analysis may have better sensitivity than bacteriological cultures, as the latter is often performed under flawed conditions. However, a study by Meyr et al. has questioned the statistical reliability of the histopathologic diagnosis of diabetic foot osteomyelitis using bone biopsies, quoting a 41% of clinically significant disagreement between different pathologists, falling short of what would be expected of a “reference standard” [16]. This highlights the controversy in histopathological patterns and findings that pathologists use as a reference to establish a diagnosis of osteomyelitis [15,17,18].

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PART VIII

SPORTS

Section 1: Prevention

Section 2: Diagnosis

Section 3: Treatment

Prevention

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QUESTION 1: What perioperative antibiotic prophylaxis should be used in patients undergoing arthroscopic surgery without the use of implants or grafts? What about patients with non-anaphylactic or anaphylactic penicillin allergy?

RECOMMENDATION: The literature neither supports nor refutes the use of antibiotic prophylaxis for routine arthroscopic surgeries, without the use of implants or grafts. For non-compromised, non-implant arthroscopy, antibiotic prophylaxis is not required. Patients with comorbidities which have been shown to cause higher risk for infection may benefit from antibiotic prophylaxis. A first-generation (cefazolin) or a second-generation (cefuroxime) cephalosporin can be used as first line, including for those with a non-anaphylactic penicillin allergy. For patients with an anaphylactic penicillin allergy, other antibiotics such as vancomycin, clindamycin or teicoplanin can be used.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The overall risk of infection following routine elective arthroscopic procedures is low (for the knee it is 0.1–3.4% [1–3] and for the shoulder it is similar at 0–3.4% [4,5]). Various patient-related risk factors that are associated with higher risk of infection have been identified including the patients being young and male, conditions resulting in immunocompromised status and history of depression [1,2]. Additional risk factors that have been identified using databases include higher body mass index, history of diabetes, longer operative time and smoking [1,2]. In these patients at higher risk of infection, special consideration should be given to the use of perioperative antibiotic prophylaxis.

In a prospective study by Qi et al. there were similar infection rates in 1,326 patients irrespective of the antibiotic prophylaxis [6]. In a randomized controlled trial (RCT) by Wieck et al., administration of antibiotics did not provide additional benefit for prevention of infection in 437 patients [7]. However, it is important to note that because of the smaller cohort size, the findings may have introduced a type II error. Similarly, a recent large database study on 40,810 simple knee arthroscopies demonstrated no association between administration of perioperative antibiotics and postoperative infection [8]. Although the rate of deep infection was lower in the antibiotic group, the difference did not reach a statistical significance.

Randelli et al. reported an infection rate of 0.16% (15 infections) in their review of a series of 9,385 shoulder arthroscopies, with a significant difference in rates between patients receiving antibiotic (0.095%) and those not receiving antibiotic (0.58%) ($p = 0.01$) [4]. Conversely, Bert et al. retrospectively analyzed 3,231 knee arthroscopies (2,780 meniscectomies) and found patients who received preoperative antibiotics had an infection rate of 0.15% compared to 0.16% in those who did not ($p = 0.59$) [9].

A recent retrospective study by Pauzenberger et al. on 3,294 arthroscopic rotator cuff repairs with implants, demonstrated a reduced infection rate from 1.54% to 0.28% in patients who received no antibiotic prophylaxis compared with those who received 2 grams of cefazolin routinely, respectively. Further, those patients who received no antibiotic demonstrated a 5.53 times higher rate of infection [10].

In elective surgery, the preferred preoperative antibiotic is a first or second-generation cephalosporin (cefazolin or cefuroxime) [11]. They are broad spectrum, cost-effective and allow newer, more expensive antibiotics to be used for more resistant organisms. Cephalosporins cover gram-positive bacteria as well as clinically important aerobic gram-negative bacilli and anaerobic gram-positive bacteria. They have good distribution in muscle, bone and synovium, achieving fast bactericidal levels after administration [11].

One placebo-controlled trial evaluating prophylactic cefazolin in 2,137 total hip arthroplasty patients showed a significant reduction in infection[12] whereas another RCT of cefuroxime compared to vancomycin and fusidic acid in 435 arthroplasty patients showed no difference in infection rate, the lack of difference may have been because of the small sample size and underpowered nature of the study [13]. Alternative first line agents are penicillins including cloxacillin and flucloxacillin [11]. In known cases of anaphylactic penicillin allergy, other agents such as clindamycin, vancomycin or teicoplanin, if available, should be considered. Clindamycin is bacteriostatic and alone has poor activity against *Staphylococcus aureus* (MRSA) so other agents (e.g., levofloxacine) may need to be coadminsitered [11]. With a non-anaphylactic penicillin allergy, a second-generation cephalosporin can still be used as there is limited cross-reactivity and penicillin skin testing can assess for a true allergy [11]. Patients colonized with MRSA should receive vancomycin or teicoplanin [14]. A recent report from Europe showed that teicoplanin was the most common agent used in high-risk patients with associated comorbidities (84% of practices), but is not available in the US, Canada or China [15].

Septic arthritis post-arthroscopy remains very rare with rates of 0.009–1.1% [16]. Despite its rarity, this complication is serious as its treatment often warrants multiple surgical procedures and prolonged antibiotic treatment, with risks of significant chondral damage and patient morbidity. Despite successful eradication of infection, the joint may develop secondary osteoarthritis and functional loss [17]. Moreover, the additional short and long-term treatment costs to the patient and hospital, is a factor to consider when using antibiotic prophylaxis [18]. However, the increasing prevalence of antibiotic resistance and the occurrence of drug-related adverse events cautions its routine use [19].

Overall, the literature on antibiotic prophylaxis for knee and shoulder arthroscopy is limited. For routine elective arthroscopy

without the use of implants or grafts in the healthy patient, there is no evidence to support the use of perioperative antibiotic prophylaxis. Antibiotics may be considered when implants are being used or when the patient has certain comorbidities which are considered risk factors for infection. A first- or second-generation cephalosporin antibiotic can be used as a first line agent, including in patients with a non-anaphylactic penicillin allergy. In patients with an anaphylactic penicillin allergy, other agents such as vancomycin, clindamycin or teicoplanin can be considered.

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QUESTION 2: Should routine methicillin-resistant *Staphylococcus aureus* (MRSA) screening be in place for patients undergoing elective sports procedures?

RECOMMENDATION: Routine MRSA screening is not warranted for patients undergoing elective sports procedures. Screening may be appropriate in higher-risk patients and patients undergoing more complex procedures.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Staphylococcus aureus (*S. aureus*) is the most frequent pathogen isolated from surgical site infections (SSIs) in patients undergoing orthopaedic procedures [1]. SSIs caused by *S. aureus* can be serious and difficult to treat, often requiring debridement with removal of orthopaedic implants. *S. aureus* resides on skin surfaces and asymptomatically colonizes approximately one-third of the population, most commonly the anterior nares [2]. Multiple studies have shown that *S. aureus* nasal colonization is a significant risk factor in developing *S. aureus* SSIs [3]. *S. aureus* is also found in the throat, axilla and groin [4], as well as in eczematous skin lesions [5]. Screening for and decolonization of *S. aureus* has been shown to decrease SSI rates in a variety of surgical specialties [6], but not specifically in patients undergoing sports procedures.

In some hospitals, 57% of isolates of *S. aureus* causing orthopaedic infection are resistant to methicillin [1]. Compared to methicillin-sensitive *S. aureus* (MSSA) causing SSI, patients with MRSA SSIs have been shown to have a higher risk of morbidity, mortality and greater hospital costs [7]. Indeed, one study showed that intranasal carriage of *S. aureus* was the only independent risk factor for SSIs following orthopaedic implant surgery [8].

Most studies evaluating MRSA screening and decolonization in orthopaedic patients were performed in elective total joint arthroplasty patients [9,10]. Other studies have also included spine patients (e.g., fusion) and trauma patients [11], and many did not state the specific type of elective orthopaedic patient included. These non-specific studies often had a minimum inpatient stay inclusion criterion, which therefore excludes almost all elective orthopaedic sports surgery cases.

Our extensive search of the literature identified a study by Kim et al. that evaluated patients undergoing sports procedures who

screened 7,019 of 7,338 (95.6%) preoperatively for MRSA. They also included patients undergoing total joint replacement and spine surgery, with a minimum one-day inpatient stay, though no details on the types of cases or numbers were provided. There were 309 (4.4%) MRSA carriers, and these patients did have a significantly higher risk of SSI compared to non-MRSA carriers (0.97% vs. 0.14%, p = 0.0162). However, the rates of infection in the sports surgery group were not reported [3].

Given the significant lack of data on the efficacy and cost effectiveness of preoperative MRSA screening in patients undergoing orthopaedic procedures in general and those receiving sports procedures in particular, the routine practice of MRSA screening cannot be recommended. Rates of infection after sports surgery procedures are generally lower than rates after arthroplasty or spine procedures, suggesting that screening strategies may prevent fewer infections and be less cost-effective in sports surgery than in other orthopaedic procedures. Very limited data suggests that screening may be considered in sports patients who will be admitted for at least one overnight stay, particularly if implants are to be used [3]. Further studies are needed to evaluate the efficacy and cost-effectiveness of screening for Staphylococcal carriage (MRSA or MSSA) in patients undergoing sports surgery procedures.

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QUESTION 3: What perioperative antibiotic prophylaxis should be used in patients undergoing arthroscopic surgery who are methicillin-resistant *Staphylococcus aureus* (MRSA) carriers?

RECOMMENDATION: MRSA carriers should be administered vancomycin or teicoplanin as antibiotic prophylaxis prior to arthroscopic surgery involving an implant and/or a graft or for patients at higher risk of infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Prevalence of MRSA colonization is increasing in some community settings, even in patients who lack traditional (or any) identifiable risk factors [1]. Surveillance studies have suggested that the colonization rate in the general population varies worldwide, with methicillin-sensitive *S. aureus* (MSSA) nasal carriers making up 20–36.4% of the population, and MRSA nasal colonization composing 0.6–6% of the population [2].

When simple arthroscopy is performed (meniscal tears, articular debridement, synovectomy and microfracture), the risk of surgical site infection (SSI) is extremely low and antimicrobial prophylaxis is not routinely recommended [3–7]. However, when arthroscopic procedures involve the use of implants, grafts, placement of several surgical incisions, prolonged operative time or knee ligament reconstruction, the SSI risk is higher than in simple arthroscopy, and prophylactic antibiotic administration may be justified [8–10]. Although the efficacy of prophylactic antibiotics in reducing SSI for major orthopaedic procedures has been proven, the role of antibiotic prophylaxis in routine arthroscopy remains controversial [3,4,11,12].

Regarding arthroplasty, some studies reveal that universal MRSA decolonization is effective in reducing the overall rate of SSIs and promoting economic gains for the health system related to the downstream savings accrued from limiting future reoperations and hospitalizations [13–15]. The American Academy of Orthopaedic Surgeons (AAOS) and Surgical Care Improvement Project (SCIP) recommend first- or second-generation cephalosporins as the prophylactic antibiotics of choice for patients who are not colonized with MRSA, with vancomycin prophylaxis reserved for those who are MRSA-colonized [16]. The addition of vancomycin or an aminoglycoside to the prophylactic perioperative antibiotic regimen results in a predicted activity of 83–97% against the most common pathogens causing SSIs [17].

Thus, based on the available evidence, it is unlikely that prophylactic antibiotics are needed for simple arthroscopic procedures

in the first instance and if the prophylaxis should be modified for patients who are MRSA carriers. In the absence of evidence, and due to the gravity of any SSI being caused by MRSA, we recommend that consideration be given to administration of vancomycin or teicoplanin as antibiotic prophylaxis prior to arthroscopic surgery involving an implant and/or a graft or for patients at higher risk of infection.

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QUESTION 4: What is the best method for anterior cruciate ligament (ACL) allograft sterilization to minimize the incidence of postoperative infections and mechanical weakening of the graft?

RECOMMENDATION: The best method for ACL allograft sterilization to minimize the incidence of postoperative infection and mechanical weakening of the graft is the use of irradiation (preferably less than 1.8 Mrad). Allografts should be harvested aseptically and fresh-frozen, whenever possible.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

An exhaustive literature review of articles published in English was undertaken to identify studies related to allograft sterilization and the incidence of postoperative infections and graft failures. The search was performed across the PubMed, Scopus, and Cochrane databases as well as Google Scholar using the following search terms: "allograft sterilization," "infections and allografts in ACL reconstruction," "complications after allograft use for ACL" and "mechanical strength of allografts." Articles in languages other than English were not reviewed, nor were articles on non-human subjects. The articles included were from 1988 until March 2018, (Levels I-IV evidence) containing evidence of graft longevity, post-ACL infections, revision rates following use of allografts and other complications associated with allograft use. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses criteria (PRISMA) were followed.

Septic arthritis after ACL reconstruction (ACLR) is a rare event, occurring in 0.14 to 1.8% of cases [1–3]. Several studies have demonstrated a lower rate of deep infection after ACLR using allograft compared to hamstring autograft tendons and equal possibilities with the use of bone patellar tendon bone (BPTB) autograft [4–8]. The increasing use of primary allograft ACLR during the last few decades can be explained by the fact that allograft offers several advantages such as shortening operative time, reducing postoperative pain, allowing a variety of grafts to choose from and avoiding harvest site morbidity [9–11].

However, allografts bring with them an intrinsic risk of contamination, which is why every possible effort must be made in order to lower this risk as much as possible.

The American Association of Tissue Bank (AATB) has made several rules in allograft procurement, sterilization and conservation, in order to guarantee a Sterility Assurance Level, which is the probability of failing the sterilization after the whole process, lower than $1x10^{-6}$ [12]. The possibility of human immunodeficiency virus (HIV) transmission is one in 1,667,600 [13], but it drops to 1/173,600 for non-processed allograft [14]. In fact, there are several steps that follow a rigid protocol to ensure a lower risk of disease transmission. The donor must be checked for known disease and an examination of the body is taken to control any sign of infection or intravenous (IV) drugs stigmata [15].

Further, the donor is screened by serology tests for viral infection (i.e., HIV type I – II, hepatitis B virus (HBV) surface antigen, HBV core antibody or hepatitis C virus (HCV) antibody) [16]. Nucleic Acid Testing (NAT) is the best test for screening HIV and HCV because seroconversion occurs 15 days after the first contact with the virus [16]. Blood cultures are necessary to check for bacterial and fungal infection. Aerobic and anaerobic cultures last for a minimum of 15 days, according with the AATB and the Food and Drug Administration [17]. The successive step is the tissue retrieval, which is performed in a sterile operating room with sterile technique [18]. After that, the graft is treated with a bactericidal-antimicrobial disinfection solution. At this stage, the graft cannot yet be considered sterile [15].

There are several sterilization techniques, which can be split into irradiation and chemical sterilization. The irradiation can be based on gamma ray or electron-based radiation. The gamma radiation works by generating free radicals and directly modifying nucleic acids, leading to genomic dysfunction [19]. Unfortunately, the first effect can damage the collagen and compromise the mechanical structure of the graft in terms of strength and elasticity [20,21]. A low dose of radiation (< 25 KGy) is able to kill the bacteria, but does not have a complete effect on the virus [22–25]. In reverse, a high dose of radiation (> 35 KGy) can kill viruses, but several studies showed that at this level of radiation, the mechanical proprieties of the graft are compromised [22,26,27].

Additionally, it is necessary to consider that there is no consensus about the fact that a low dose of radiation does not damage the graft. Park et al. reviewed 21 publications and found a total of 1,453 ACLR with allograft (415 low-dose irradiated; 1,038 non-irradiated) [28]. The authors found worse functional outcomes and greater rates of re-rupture in patients receiving irradiated allograft. However, in the single publications, the result was good to excellent in both groups, and not all of the functional scores favoured the non-irradiated group as the International Knee Documentation Committee score was higher in the irradiated group [28].

There are several publications suggesting that a low dose of gamma radiation does not affect the biomechanical properties of the graft [29,30]. However, other studies find the opposite [31–33].

Furthermore, other studies suggest the efficacy of radioprotective solution (i.e., propylene glycol, dimethyl sulfoxide, mannitol and trehalose) in protecting the graft from even high doses of gamma radiation [20,34].

An alternative system is electron-based radiation, which has a lower penetration (8cmH_2O vs. 30cmH_2O), and a lower time is required for the sterilization (seconds vs. hours) compared to gamma irradiation. Good results have been demonstrated if used in combination with other tissue-protective measures (i.e., low temperature or carbon dioxide) [35]. Further studies are required to fully understand the effectiveness of this method.

Chemical sterilization is another option, however, some of these processes should be avoided. For example, ethylene oxide can cause post-implantation synovitis, cysts and graft failure [36,37] and iodophor rinse followed by water is not uniformly viracidal [37].

An effective solvent is paracetic acid (PAA), which does not change the strength or elasticity of the graft [38] even if it seems to be correlated with a delay in the biological remodelling, and thus can cause a reduction in early knee stability (first three months) [39].

In the absence of any definitive evidence that addresses both the mechanical strength as well as anti-infective properties in allografts, we would propose that if an allograft is the only choice available, it should preferably be fresh-frozen, aseptically harvested and subjected to less than 1.8 Mrad of irradiation. Indeed, the majority of tissue banks use combined methods (i.e., Crylife Inc., Biocleanse, Allowash, Tutoplast process, the clearant process, etc.).

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QUESTION 5: Should autograft or allograft be soaked in an antiseptic or antibiotic solution prior to implantation during anterior cruciate ligament reconstruction (ACLR)?

RECOMMENDATION: Yes, autograft tissue should be soaked in an antibiotic solution prior to implantation during ACLR.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 91%, Disagree: 9%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

Infection after ACLR is rare but can cause serious complications [1]. Contributing factors that may predispose to infection include diabetes, smoking, increased time of surgery and tourniquet inflation, additional or larger incisions for arthroscopic portals and the use of a drain [2].

The use of a preoperative prophylactic antibiotic has been previously established to reduce infection rates in orthopaedic surgery procedures [3]. Historically, ACL allografts have been associated with a higher risk for infection. However, a recent systematic review reported no difference in infection rates between allograft and autograft tissue for ACLR [4]. Further, hamstring autograft grafts have been reported to have a higher incidence of infection compared to both allografts and bone-tendon-bone (BTB) patellar tendon autografts [5–7].

Among the published studies, there are strong evidences that pre-soaking of hamstring grafts in topical vancomycin reduced the rate of postoperative infection when compared to intravenous (IV) antibiotics alone.

Vancomycin has been reported for its use for local antibiotic infusion into joints [8]. Vertullo et al. investigated the utility of soaking hamstring autografts with vancomycin before implementation during ACLR. In their investigation, both patient cohorts received preoperative IV antibiotics while one group additionally received a pre-soaked vancomycin graft. A statistical difference in infection rates was noted between the two patient groups as the preoperative IV antibiotic-only group reported an infection rate of 1.4% compared to a 0% rate for the group with the vancomycin-soaked allograft [9].

Pérez-Prieto et al. performed a similar study. Both patient cohorts received preoperative IV antibiotics while one group additionally received a pre-soaked vancomycin graft. However, in this series, BTB autografts were included as well. The group without vancomycin saturation of the graft had an infection rate of 1.85% while the group of patients who received systemic antibiotic prophylaxis and graft pre-soaking with vancomycin did not experience any infections (0%) [10].

Phegan et al., reporting on the use of vancomycin-soaked hamstring autografts, noted no infections in a series of 1,300 patients receiving prophylactic vancomycin pre-soaked hamstring grafts in addition to systemic antibiotics [11]. Additionally, Yazdi et al. reported using gentamicin irrigation solutions in conjunction with preoperative IV antibiotics with an infection rate of 0.57% compared to an infection rate of 2.1% in patients receiving only IV antibiotics. All patients in this series received autologous grafts [12].

Vancomycin has activity mostly against gram-positive microorganisms, while gentamicin is a broad–spectrum antibiotic targeting both gram-positive and gram-negative microorganisms [11].

Due to the high impact of literature supporting the use of soaking autograft tissue in an antibiotic solution prior to implantation during ACLR, we conclude that soaking autografts in antibiotic solution is an effective treatment in reducing infection postoperatively.

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QUESTION 6: What is the most appropriate/effective sterilization method of an anterior cruciate ligament (ACL) graft dropped on the operating room (OR) floor during ACL reconstruction (ACLR)? Should the tissue instead be disposed and alternate graft acquired?

RECOMMENDATION: Rinsing the contaminated graft in a 4% solution of chlorhexidine gluconate is the most effective decontamination method in the event that an ACL graft is dropped on the OR floor. When a chlorhexidine gluconate solution is used for decontamination of the dropped ACL graft, the subsequent rates of infection are very low, suggesting that there is no need to dispose of the ACL graft.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Injuries to the ACL are among the most common injuries to the knee, with reconstruction being the preferred method of treatment when functional instability is present [1]. Autografts are frequently used for ACLR, but it has been shown that the use of autografts is associated with contamination as a result of the harvesting and manipulation process [2]. Contamination of the autograft can also occur accidentally, by dropping the graft on the OR floor or allowing it to come into contact with non-sterile surfaces. In fact, a 2008 survey showed that 75% of plastic surgeons had dropped an autograft on the OR floor at least once [3]. In 94% of those cases, the autograft was decontaminated and the operation was completed. This protocol may put the patient at risk for the development of an intraoperative infection if proper decontamination procedures are not followed. This is particularly concerning given the sheer volume of ACL autograft reconstructions done each year, which has led to a variety of case studies to attempt to identify the best method for sterilizing a dropped autograft during ACLR.

Numerous studies have shown that a contaminated autograft can be effectively decontaminated by rinsing it in a 4% chlorhexidine gluconate solution [4–8]. There is some discrepancy regarding the length of time that a graft should be rinsed in the chlorhexidine solution, with 90 seconds [8], three minutes [6,7], 15 minutes [9] and 30 minutes [4] all being recommended. Khan et al. determined that rinsing a contaminated autograft in a 4% chlorhexidine gluconate solution was the most effective decontamination technique in a systematic review of seven studies [10]. The studies included used samples from a variety of sources (fresh-frozen, autograft, cadaver) and they found that 98% of contaminated grafts soaked in chlorhexidine showed no bacterial growth [10].

Bacitracin, polymyxin B and povidone iodine were additional proposed methods of decontaminating a dropped graft, but there were conflicting recommendations regarding their use. Of note, bacitracin was shown to be highly effective in decontaminating hamstring autografts [6,7], but it did not decontaminate bone-patellar tendon-bone grafts [11]. The clinical relevance of the latter observation has not been explored further. While a povidone iodine rinse was found to be a useful method of decontamination when used on grafts dropped on the OR floor, it was ineffective on samples artificially contaminated with *Staphylococcus aureus* and *Pseudomonas aeruginosa* [12].

There is a lack of patient outcomes data and randomized control trials on the subject, as well as some discrepancy regarding the length of time a graft should be rinsed prior to implantation. However, there is agreement between numerous case studies indicating that rinsing a contaminated ACL graft in a 4% chlorhexidine gluconate solution is an effective and appropriate decontamination method.

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QUESTION 7: Does the use of a tourniquet influence the incidence of surgical site infection (SSI) following arthroscopic surgery of extremity joints?

RECOMMENDATION: No. A direct relationship between use of a tourniquet for arthroscopic surgery of the extremity joints and the incidence of SSI has not been established.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The use of a pneumatic tourniquet during arthroscopy is a popular intraoperative measure to control bleeding, improve visualization, ease surgical procedures and possibly shorten the operative time, especially in knee procedures. For several decades, various studies have suggested that tourniquet application may result in an increased risk of postoperative pain, nerve paralysis, swelling, joint stiffness and functional weakness bringing into question the value of tourniquet use [1,2]. However, two meta-analyses found no difference in functional outcomes and general complications among patients undergoing arthroscopic surgery with and without the use of tourniquet [3,4]. Therefore, the use of tourniquets remains at the discretion of treating surgeon. A survey of the American Orthopaedic Society of Sports Medicine, Arthroscopy Association of North America and Delhi Arthroscopy Society members revealed that the majority of surgeons preferred to use tourniquet during arthroscopy surgery, thus making comparison of the outcome of these patients without the use of tourniquet somewhat difficult [5].

The potential influence of tourniquet use on the risk of subsequent SSI following arthroscopic surgery is not clear. If the tourniquet use results in a higher rate of SSI, a possible mechanism could be related to the effect of ischemia on antibiotic diffusion in the bone marrow. Administration of antibiotic while the tourniquet is inflated is unlikely to allow for proper diffusion of the antibiotics to the operated extremity and the joint. Because of the latter issue, a ten-minute delay between antibiotic administration and inflation of the tourniquet is proposed to allow the antibiotic to reach the required minimal inhibitory concentration (MIC) level in the operated joint [6].

Regarding the correlation between tourniquet use and the risk of infection after joint arthroscopy, no randomized controlled trials (RCTs) with this primary outcome were found. The available high-level studies on knee arthroscopy were underpowered due to the rarity of SSI, while no meta-analyses performed a pooled analysis of SSI events following tourniquet and non-tourniquet arthroscopic surgery [3,4]. Additionally, few single-center series of knee arthroscopies analyzed the risk factors for SSI. Sherman et al. retrospectively evaluated 2,640 arthroscopies, and did not report a direct correlation between tourniquet use and postoperative complications, including infection. However, a higher risk of postoperative complications was found only in patients older than 50 years and in a tourniquet time longer than 60 minutes [7]. Reigstad et al., focusing on SSI, reported two superficial infections after 876 simple arthroscopies (0.23%), mostly after medial meniscectomies, and failed to identify a significant correlation with tourniquet use. Rather, they rather reported a higher incidence of complications in cases of prolonged surgical time [8].

Also, Vachal et al. reported six SSIs after 908 anterior cruciate ligament reconstructions (ACLR) (0.7%), identifying previous surgeries as the only significant predictor for SSI [9]. The risk of infection has been specifically investigated in two large multi-centric series of ACLR, the Multicenter Orthopaedic Outcome Network (MOON) cohort and Kaiser-Permanente registry including 2,198 and 10,626 patients, respectively [10,11]. However, they were limited to the inclusion of tourniquet use and operative time in the multivariate logistic regression. The same limitation has been disclosed in other large multi-centric cohorts involving up to 700,000 patients undergoing knee arthroscopy [12,13].

Regarding elbow, wrist and ankle joints, few studies evaluated arthroscopic procedures without the use of the tourniquet, thus solid conclusion cannot be drawn regarding the impact of tourniquet use and SSI after ankle, elbow or wrist surgery [14–17].

Based on the available literature, no direct relationship between tourniquet use and SSI has been reported. What is clear is that there is a direct link between surgical time and the risk of subsequent infection in arthroscopic surgery of extremity joints. Thus, the use of tourniquets should be subordinated to the surgeon's preference and experience, and balanced with the patient's characteristics, comorbidities and the complexity of the procedure to limit the surgical time. When antibiotic prophylaxis is planned, the tourniquet should be inflated at least ten minutes after its administration.

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QUESTION 8: What strategies should be employed to minimize recurrent infection of a previously infected joint during subsequent joint reconstructive (non-arthroplasty) procedures?

RECOMMENDATION: We recommend that joints with remote or recent history of infection be aspirated and the synovial fluid analyzed for the presence of infection. The affected joint should not exhibit any clinical signs of infection such as erythema, swelling, warmth and others at the time of planned reconstruction.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Our extensive literature search did not reveal any studies specifically focusing on the prevention of recurrent infection in previously infected joints during reconstructive (non-arthroplasty) procedures. It is, however, well-established that previous septic arthritis is a risk factor for subsequent surgical site infection (SSI) and periprosthetic joint infection (PJI) [1–4]. Furthermore, different studies described the risk factors for developing septic arthritis, such as morbid obesity, tobacco use, inflammatory arthritis, chronic kidney disease, diabetes and hemodialysis [5–7]. Cancienne et al. reported in their case-control study of over 530,000 shoulder arthroscopies that prior steroid injection, revision surgery and malnutrition were independent risk factors for infection [8].

Multiple PJI and SSI risk mitigation strategies may be considered in a patient with remote or recent history of joint infection undergoing a reconstructive non-arthroplasty procedure [1–3,9,10]. These are discussed in further detail below.

- Medical optimization: Consider optimization of modifiable risk factors such as treatment of any systemic or local infection, correction of malnutrition, weight reduction in patients with morbid obesity (> 40 kg/m^2), treatment of vascular insufficiency, smoking cessation, correction of hyperglycemia and preoperative cessation of immune-modifying medications [10].
- Antibiotics: Administer prophylactic antibiotics to reduce the risk of recurrent infection. In patients with previous methicillin-resistant *Staphylococcus aureus* (MRSA) infection, the addition of vancomycin or teicoplanin as perioperative antibiotic prophylaxis should be considered [10,11].
- Skin preparation: Preoperative surgical site preparation using soap (antimicrobial or non- antimicrobial) or an antiseptic agent on the night before the operative day should be considered [2,10].
- Particle-free operating environment: While there is no definitive evidence for the efficacy of laminar air flow in non-arthroplasty surgery, the number of theatre personnel and operating room traffic should be minimized to reduce the risk of recurrent infection [10].
- Respect the soft tissue: Meticulous surgical technique, proper wound closure and an effort to reduce the surgical time may help minimize the risk of recurrent infection [10,12].
- Intraoperative wound irrigation: Copious intraoperative irrigation is considered an effective strategy to reduce the number of pathogens in the surgical wound [10].
- Wound management: Antimicrobial dressings may reduce the risk of SSI [10,13].

More recently, pre-soaking of hamstring tendon autograft in a vancomycin solution has been shown to reduce septic arthritis following ACL reconstruction. As such, we recommend soaking the autograft (and possibly allograft) in an antibiotic solution such as vancomycin when used in previously infected knees [14–17].

In the absence of specific literature related to the above question, we recommend that all measures are taken to ensure that infection in the affected joint is resolved, which includes absence of erythema, swelling and so on. In addition, the affected joint should be aspirated and the synovial fluid analyzed for signs of infection.

During the reconstruction of the previously infected joint, all available strategies for prevention of infection should be implemented.

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QUESTION 9: Is the surgical management of a patient with infection following anterior cruciate ligament reconstruction (ACLR) an emergency, or can the patient be optimized prior to surgical intervention? If so, what needs to be optimized?

RECOMMENDATION: Infection following ACLR is not a surgical emergency in most cases. Sepsis associated with infected anterior cruciate ligament (ACL) requires an emergency treatment. Most surgeons agree that surgical intervention should take place without delay, on a prompt basis, preferably on the same day as the clinical presentation of an ACLR infection. The patient's condition needs to be optimized prior to surgery.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infection following ACLR is a rare event affecting up to 2.25% of patients, but it is a serious complication [1–15]. Surgical management of ACLR infections is frequently discussed in the literature, but the timing of surgical intervention is not clearly stated in the majority of these publications [3,4,6,10–12,16–18].

A few studies have addressed the issue of timing of surgery. A study by Schuster et al. stated that the surgery should be performed on the day of admission [19]. Another study by Mouzopoulos et al. also declared that the infection should be treated without delay [20]. In a review article, Wang et al. reported a summary of various studies by stating a recommendation for immediate operative treatment [21]. Torres-Claramunt et al. also reported that the generally-accepted treatment is "arthroscopic lavage, performed as soon as possible" [22]. It is known that articular cartilage degrades rapidly and loses nearly half of its glycosaminoglycan and collagen composition in the first week of a joint infection [23,24]. Therefore, a significant delay should not be experienced in the initiation of surgical treatment in patients presenting with an infection of ACL reconstruction.

The major drawback in the literature is that almost all of the studies published on infection following ACLR have been retrospective reviews. It is well-established in these studies that infection following ACLR can rarely be a life-threatening emergency. A timely and well-planned course of action based on clinical and laboratory data and microbiological findings is recommended. Graft retention has been shown as a goal along with articular cartilage protection, so lengthy delays should be avoided [1,3,6,11,13,17,18,25,26].

A protocol for patient optimization prior to surgery has not been clearly established. Clinical examination and aspiration of the knee joint is recognized as the first step in diagnosis at initial patient presentation with a suspected postoperative ACLR infection. It is also generally reported that broad-spectrum antibiotics, preferably cephalosporins, should be started as soon as possible after joint aspiration is performed [10,12,15,16,19,20,22,27]. The antibiotics should target coagulase-negative *Staphylococcus* (CNS) and *Staphylococcus aureus*, as these are the most common infecting organisms. Antibiotic therapy should be modified as soon as culture results identify the specific pathogen and the susceptibility.

Blood tests for infectious and inflammatory markers, such as white blood cell count, erythrocyte sedimentation rate and C-reactive protein, should also be conducted on the day of presentation.

This will add to the initial clinical data and offer serial information to monitor infection eradication [19–22]. Clinical records of the patient should be reviewed to identify the nature of the prior operative procedure, type of graft, method of fixation and additional meniscal or cartilage procedures, if performed [1,4,6,15,19].

As with all surgeries, comorbidities should be medically managed. This may include better control of hyperglycemia, correction of anticoagulation, correction of anemia and other conditions that may adversely influence the outcome of surgical procedure.

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QUESTION 1: Should culture samples be taken during arthroscopic treatment of a knee joint infection? If so, how many and from which area in the joint?

RECOMMENDATION: Yes, culture samples should be taken during arthroscopic treatment of a knee joint infection. We recommend that at least three culture samples from different sites be taken.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infections of the knee joint can occur either from hematogenous spread or directly due to local trauma or a medical intervention. Infections after an arthroscopy for anterior cruciate ligament reconstruction (ACLR) or meniscal pathology are reported throughout the literature [1–18]. Infection can also occur in healthy native knees [13,19–24]. Sending intraoperative samples of synovial fluid and tissue for microbiological analysis is commonly reported in the literature [1–12,14–24], with only one study reporting no intraoperative samples for culture [13]. Two studies described the number of samples taken during the arthroscopy [11,19]. In both of the studies, five samples were taken and sent for culture. Unfortunately, no studies described an optimal area of the joint from which to take the samples.

When considering the existing research, it can be concluded that samples should be taken during arthroscopic treatment for a knee infection. However, based on the review of the literature, no conclusion can be drawn about the number of samples.

There is more research describing the number of samples to be taken during debridement in periprosthetic joint infection (PJI). In their study on 113 PJIs, Gandhi et al. concluded that the optimal number of cultures needed to obtain a positive test result was four (specificity = 0.61, sensitivity = 0.63). Furthermore, they stated that increasing the number of samples increases specificity but reduces sensitivity [25]. In the same study, the samples were collected from representative areas of the joint, including, but not limited to, synovium, intramedullary tissue, prosthetic interface and tissue from the adjacent bone [25].

During the previous consensus meeting in 2013, it was concluded that three to six samples should be obtained intraoperatively in suspected PJI cases [26]. Similarly, other authors confirmed that three to five samples should be obtained from deep tissues during surgery for suspected PJI [27,28].

There is no agreement about the area of the joint the samples should be taken from during arthroscopic treatment of septic knee arthritis. In their review, Bauer et al. reported that the samples should be taken from the deep tissue [29]. In their systematic review, Mouzopoulos et al. suggested that during arthroscopic treatment of septic ACLR, samples for culture should be taken from multiple areas, such as synovial lining, graft, femoral and tibial tunnel [30].

Based on the available data, no definitive conclusion can be drawn on the number of samples needed and the area of the joint they should be taken from during arthroscopic treatment of septic knees. Studies based on PJI were considered, as well as literature reviewed on knee septic arthritis after ACLR. Based on this data, it may be extrapolated that at least three samples should be collected during arthroscopic treatment of knee joint infection. Furthermore, they should be taken from multiple areas of the joint: graft, synovial lining and from the femoral and tibial tunnels when present. It is reasonable to also collect samples from other areas, such as the medial and lateral gutters and the suprapatellar pouch.

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QUESTION 2: What diagnostic "algorithm" should be used to diagnose infection following anterior cruciate ligament reconstruction (ACLR)?

RECOMMENDATION: The "algorithm" to diagnose postoperative infection in patients with ACLR should include clinical presentation, serological tests including C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) and analysis of the synovial fluid aspirate including gram staining and culture.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Postoperative infections following ACLR are rare, occurring in only 0.14–5.7% of cases [1–5]. As a result, clinical studies are limited and have small sample sizes. However, the general consensus is that the clinical presentation, laboratory blood tests, (specifically (CRP) and ESR) and synovial fluid aspiration analysis are essential for the diagnosis of infection after ACLR [6–13]. Magnetic resonance imaging can detect joint effusion, synovitis, edema of adjacent soft tissues and bone marrow, bone erosions, sinus tracts and soft tissue abscesses, though this has only been reported in one study [14].

Features of the clinical presentation that raise suspicion of infection include fever, malaise, sudden change in knee pain of moderate intensity, local incision drainage, local warmth, local swelling, erythema, decreased knee range of motion and inguinal lymph node enlargement, though each of these symptoms is not present in all cases [8,11,15–17].

Laboratory blood analysis should be included in the diagnosis of infection after ACLR. Interpretation of results can be challenging, as elevated levels are routinely seen postoperatively, (typically peaking by postoperative day three), as a result of the surgical trauma [3,7,13,18]. C-reactive protein levels, which increase within six to eight hours after infection, have been shown to have the highest sensitivity and specificity. Reported average C-reactive protein levels in patients after ACLR with knee infection range from 55.8 to 203 mg/L (range, 10-400 mg/L) (normal 0-0.5 mg/L) [11,15–17]. ESR levels typically rise within 24 to 48 hours [19–21]. Average ESR values in patients with knee infection after ACLR range from 57 to 76 mm/h (range, 9-108 mm/h) in the literature (normal 1-10 mm/h) [11,13,15,17,18]. Peripheral white blood cell count has also been shown to be elevated in patients with postoperative knee infection after ACLR (9.1 to 10.8 x 109/L), though this is not a consistent finding in the majority of patients [13,15,17]. Polymorphonuclear neutrophils (average 71.7%) and fibrinogen levels (average 774.7 mg/mL) have also been assessed and shown to be elevated in patients with ACLR and postoperative knee infection [13].

Gross inspection of knee joint aspiration commonly reveals turbid, yellow-green synovial fluid.[3] Microbiological analysis of synovial fluid aspirate is the most widely studied diagnostic method for septic arthritis [1,6,8,9,19,22,23]. Analysis includes gram staining, leukocyte counts, aerobic and anaerobic cultures and antibiotic sensitivities [6,13]. Positive leukocyte counts of aspirated knee fluid in knee infections after ACLR have also been reported [average 91,000 (range 64,000 to 129,000)] [6,11]. Several retrospective studies have shown that in most cases synovial fluid bacterial cultures are positive to coagulase-negative Staphylococci (*Staphylococcus epidermidis*), *Staphylococcus aureus*, *Streptococcus non-hemolytic*, *Staphylococcus schleiferi*, *Escherichia coli* or Propionibacterium in acute septic arthrosis [6,11,13,15,17–19,23,24].

Overall, there is consensus that the diagnostic algorithm for postoperative knee infection following ACLR should include sudden change in history and presentation to include change in knee pain profile, swelling and range of motion, in addition to elevated CRP

and ESR blood laboratory test values and synovial fluid aspirate microbiological analysis, though due to the rarity of its occurrence and limited number of studies and sample size, the recommendation is only of moderate strength.

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Treatment

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QUESTION 1: Can arthroscopy be used for management of patients with acute sepsis of the native knee joint?

RECOMMENDATION: Yes. Arthroscopy can be used for treatment of acute sepsis of the native knee joint.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

An extensive literature search was conducted to identify all publications related to the use of arthroscopy for management of acute septic arthritis of the native knee. A total of 18 publications were identified for review and of these, 1 was excluded as the cohort included patients with periprosthetic joint infection. Three publications were not available despite all attempts to retrieve them. Fourteen papers were reviewed in full, including five publications reporting results from the pediatric population. There was one randomized controlled trial by Peres et al., and the remaining studies were retrospective reviews [1]. In the management of septic arthritis of the native knee, the two key points to address are successful clearance of infection and minimization of complications. The pediatric papers have been reviewed separately.

Adults:

Seven papers compared arthroscopic management with arthrotomy and two papers reported only on arthroscopic results.

Jeffe et al. described successful infection clearance at four months with one procedure in 75.8% (25/33) treated with arthroscopy and 80.9% (38/47) treated with arthrotomy. This difference was not statistically significant [2]. After further statistical analyses, failure in the arthroscopic group was associated with infection being caused by methicillin-resistant *Staphylococcus aureus* (MRSA) (five out of eight failures). Similar success rates were reported by Balabaud et al. accounting for 72% (16/21) for arthroscopy and 84% (16/19) for arthrotomy [3]. Böhler et al. reported significantly lower reoperation rates and significantly better functional outcomes in patients treated arthroscopically. They achieved clearance with one procedure in 95.1% (39/41) treated arthroscopically and 79.3% (23/29) treated with arthrotomy [4]. Dave et al., with follow-up of up to 7.2 years, reported success rates of 77.8% (28/36) with arthroscopy and 60% (6/10) with arthrotomy [5]. They found no relationship between using arthroscopy and the need for multiple procedures but they did report a statistically significant relationship between the number of hours between onset of symptoms and time to index procedure and the need for multiple procedures in the group as a whole [5].

Wirtz et al. had higher success rates, at 93% (25/27) with arthroscopy and 83% (20/24) with arthrotomy [6]. A large study by Johns et al. found a 2.6 times higher chance of needing further surgery in the arthrotomy group, although overall their success rates from the primary procedure were lower than other studies with a reported success rate of 50% (59/119) for arthroscopy and 29% (12/42) for arthrotomy [7].

These results support the use of arthroscopy as the initial treatment, and are backed up by the randomized controlled trial by Peres et al. with two-year follow-up reporting 100% (10/10) success rate for arthroscopy compared to 82% (9/11) for arthrotomy [1]. However, the small sample size, and the low rate of culture positivity (at 47.6%) raises concern that some of these patients may have suffered inflammatory conditions and were not truly infected.

Complications:

Complications other than reoperation were not uniformly reported in all papers. On univariate analysis by Bovonratwet et al., higher mortality and serious adverse events were associated with arthroscopy and higher transfusion rates and minor adverse events were encountered after arthrotomy [8]. On multivariate analysis, controlled for age and American Society of Anesthesiologists (ASA) grade, there was no statistically significant difference between the risk of all adverse events or readmission. Johns et al. [7] and Böhler et al. [4] reported median knee range of motion post-arthroscopy being statistically significantly higher, in contrast to other studies discussed above. However, they did report pain at 7 and 14 days being statistically significantly better in the arthroscopy group, and reported significantly more local warmth and redness in the arthrotomy group at 1 week.

Pediatric Cases:

In the management of pediatric patients with septic arthritis of the knee, the results from five retrospective reviews also supported the use of arthroscopy. However, positive culture results ranged from 48% to 62.5%, when documented. Johns et al. concluded that arthroscopy was more successful that arthrotomy in reducing return to theatre and regaining knee function earlier. However, on long-term follow-up (mean 6.9 years) they found no significant difference between the groups [7]. Success following the first procedure was reported in 11/11 (100%) for arthroscopy and 8/13 (61.5%) following arthrotomy [7]. The other four papers on managing pediatric patients only reported results of arthroscopy. Success rates were 54/56 (96%) from Agout et al. [9], 5/5 (100%) from Sanchez and Hennrikus [10], 15/16 (93.8%) from Ohl et al. [11] and 16/16 (100%) from Stanitski et al. [12].

Complications other than return to operating room were reported in all papers, but not uniformly. At 6.9 years of follow-up, Johns et al. found no difference between the Knee Injury and Osteoarthritis Outcome Score (KOOS) and Lysholm scores, range of movement, leg length discrepancy (LLD) and gait between the arthroscopy and arthrotomy groups [7]. At three weeks follow-up, Ohl et al. reported that all patients had resumed normal activities and

no abnormalities on radiographs [11]. Agout et al. [9], Sanchez and Hennrikus [10] and Stanitski et al. [12] reported no pain, symmetrical range of movement, no radiographic changes and < 5mm of LLD in all patients at final follow-up.

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QUESTION 2: What type of lavage solution should be used in patients with a native knee infection being treated with arthroscopy?

RECOMMENDATION: We recommend that high volumes of saline without antibiotics should be used as the arthroscopic lavage solution for native knee infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infection of the native knee can be treated surgically by open or arthroscopic methods [1–3]. Arthroscopic lavage techniques have been used widely, since the introduction of arthroscopic debridement offers the benefits of smaller incisions, decreased tissue damage and lower reinfection rates compared to open methods [1–3]. Arthroscopic treatment yields good to excellent results, though there are a limited number of comparative studies in the literature (many with small sample sizes) [1–10]. Irrigation aids in the removal of debris and decreases the intra-articular concentration of chondrolytic enzymes better than needle aspiration alone [11,12].

There is a general consensus in the literature supporting high-volume (10 to 15 L) arthroscopic lavage with saline combined with intravenous antibiotics both in pediatric and adult patients for septic arthritis [1,3,9,10,13–25]. Based on microbiological findings, lavage plus intravenous antibiotics appears sufficient to eradicate *Staphylococcus aureus*, the most common cause of septic arthritis of the native knee [7]. Two studies with larger patient numbers support saline irrigation without intra-articular antibiotics as the lavage solution of choice [2,7]. A large number of other studies described using saline lavage solution for arthroscopic treatment of knee sepsis, with an average volume of 10.1 L [6,9,17,18,20,22,26–30]. Shinjo et al. compared the effects of two common arthroscopic irrigation solutions on meniscus tissue cells, and demonstrated that Ringer's lactate solution better maintained human meniscus cell integrity than the isotonic saline [31].

Additionally, there is a lack of agreement on the use of intra-articular antibiotics despite their frequent use during arthroscopic treatment of infected native knees in clinical practice without recommendation, thus warranting further investigation [32,33]. While some are proponents of intra-articular antibiotics, others are concerned about resultant chemical synovitis and potential chondral toxicity, not mentioning the risk of increasing antibiotic resistance [5,34,35]. Only one study by McAllister et al. specifically described using an antibiotic-loaded Ringer's lactate solution during arthroscopic treatment of four postoperative septic knees following anterior cruciate ligament reconstruction. The antibiotic name was not mentioned, but they reported a 100% eradication rate for infection [17]. The use of continuous irrigation-suction drains with antibiotics added to the irrigation solution has been both supported and refuted in the literature [4,5,34,36–38]. Some studies support the use of continuous suction irrigation drains with saline, whereas others caution against their use due to concerns of secondary infection [2,4–7,13,14,14,14,34,36,39].

In conclusion, other than saline, there is limited data to support the use of other arthroscopic lavage fluids for treatment of native knee infections and further comparative clinical studies are needed.

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QUESTION 3: Should a synovectomy routinely be performed during arthroscopic treatment of an acute infection following anterior cruciate ligament reconstruction (ACLR)?

RECOMMENDATION: No. Total or partial synovectomy should be reserved for cases of severe or chronic infection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

According to Gaechter and the proposed classification, the synovial membrane serves as a natural barrier in infection [1,2]. As a result, a primary synovectomy should be avoided in acute infections except for later stages [1,2]. The four stages of joint infection described by Gaechter were:

Stage I: Synovitis, turbid fluid, possible petechiae

Stage II: Fibrin clots, franc pus

Stage III: Thickening of the synovial membrane (up to several centimeters), multiple pouches due to adhesions

Stage IV: Pannus. Aggressive synovitis, radiographically visible changes, subchondral erosions

Klein et al. suggested a stage-oriented therapy for the treatment of bacterial joint infections in 1989, based on three stages of infection, which largely coincided with the stages I to III according to Gaechter [3].

An extensive irrigation of the joint and removal of all hematoma, fibrin deposits and partial synovectomy should be performed when synovitis is present [4,5]. In the presence of cartilage erosions in the joint or additional septa, a subtotal synovectomy is recommended [3]. Other studies advocate for a synovectomy during the first irrigation and debridement procedure, with fair results [6,7]. Zalavras et al. reported a successful outcome following a complete synovectomy [8]. More recent papers again recommend a synovectomy only in stages III and IV [9].

Prompt recognition of an infection and intervention with irrigation and debridement alone can prevent the need to remove ligament grafts and hardware. Therefore, a synovectomy should not be routinely performed during arthroscopic treatment of an acute infection following ACLR. However, this issue has not been well studied, and further studies are needed to address the influence of synovectomy in the management of infected ACLR.

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QUESTION 4: Should the graft and all hardware be removed in the treatment of patients with an acute infection following anterior cruciate ligament reconstruction (ACLR)?

RECOMMENDATION: The initial approach to an acute infection following ACLR should be arthroscopic irrigation and debridement, retention of a stable graft and hardware and intravenous antibiotic therapy.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The incidence of septic arthritis after anterior cruciate ligament (ACL) surgery is low (0.14 to 2.25%) [1]. In acute postoperative infections, graft and hardware removal versus retention remains controversial with the goal being to eradicate the infection, preserve the articular cartilage and retain a functioning graft.

A prospective study by Abdel-Aziz et al. analyzed 2,560 ACL procedures with 24 cases of septic arthritis, with a mean follow-up of five years. In all patients, arthroscopic surgical debridement was performed (average three procedures), followed by intravenous antibiotic treatment. In all 24 cases, infection was eradicated with this protocol. No functional differences were found compared to control group according to Lysholm, International Knee Documentation Committee (IKDC) and Knee Injury and Osteoarthritis Outcome Score (KOOS) ratings [2]. Likewise, Schuster et al. reviewed more than 7,000 ACLRs, identifying a total of 36 cases of acute postoperative infections. The graft was retained in all but one case (97.2%) with a mean of 2.25 (+/-1.22 SD) procedures required to treat the infection [3].

In a meta-analysis, Kuršumović et al. reported a success rate of 85% for graft retention and infection eradication [4]. They analyzed 16 studies with a total of 147 knee infections after ACLR. Increased rates of failure were seen in cases with persistent infection requiring subsequent procedures, from 4.4% with one arthroscopic debridement, to 11.4% with two procedures, or 25% with more than three surgeries [4]. In a similar systematic review, Makhni et al. analyzed 19 studies with a total of 203 cases of septic arthritis following ACLR and reported a success rate with graft retention of 78% [5].

Wang et al. also demonstrated success after serial irrigation and debridement and intravenous antibiotics. In addition, they demonstrated a greater graft retention rate when infection was diagnosed and treated immediately (< 7 days) suggesting a crucial time constraint to treatment [1].

Therefore, the data suggests that the initial approach to acute postoperative infection after ACLR should be to attempt to retain the graft and hardware. However, there are cases in which removal should be considered, which may include presence of gross purulence, when infection is resistant to multiple irrigations and debridement, possible bony involvement of the tibia or femur and/or a non-functional graft [6,7].

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QUESTION 5: How many arthroscopic procedures are reasonable for the management of an infected anterior cruciate ligament reconstruction (ACLR) prior to considering graft and hardware removal?

RECOMMENDATION: Prior to considering stable graft and hardware removal, at least two arthroscopic procedures are reasonable for the management of an infected ACLR. There is evidence for successful treatment and graft retention with further arthroscopic procedures.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Septic arthritis after arthroscopic ACLR is rare with an overall frequency to be around 1% [1–4]. However, when it does occur, it is a potentially serious event with possible sequelae of osteomyelitis, arthrofibrosis and damage to the articular cartilage leading to osteoarthritis [5–7]. Although a rare occurrence, surgeons who routinely perform this procedure are likely to encounter this complication during their career [8].

Repeated arthroscopic lavage is part of the algorithm to treat infection after ACLR [4]. The number of arthroscopic procedures necessary is guided by clinical and laboratory progression as well as organism virulence and patient-related factors such as age and pre-existent comorbidities [3,9]. In a study by Bostrom Windhamre et al., patients suffering from septic arthritis after ACLR underwent a mean of 3.7 interventions (range 1 to 11) [10]. Arthroscopic lavage was repeated if the patient had persistent fever, swelling and a C-reactive protein level greater than 50 mg/L. In a study of 90 cases of septic arthritis after ACLR conducted by Saper et al., arthroscopic irrigation and debridement was performed in 95.5% (86/90) of cases with an average of 1.51 procedures [2].

According to Abdel-Aziz et al., a median of three (range 1 to 6) repeated arthroscopic debridement and synovectomy procedures were required to eradicate infection [3]. In another study by Schulz et al., irrigation and debridement successfully treated the infection with a mean of 2.2 procedures with no recurrences of septic arthritis or bone infection [11]. Kim et al. presented 146 patients producing 111 (78.1%) positive intraoperative cultures. *Staphylococcus epidermidis* was identified in 46 knees (41.4%) with *Staphylococcus aureus* found as the second most common organism and presented in 38 knees (34.2%) with infection after ACLR [12]. This report differs from the previous general consensus that *Staphylococcus aureus* was the most commonly reported organism in ACLR infection [9].

In their study of 147 patients with infections of the knee, Wang et al. noted that coagulase-negative *Staphylococcus* (CNS) was the most common pathogen and represented 45.6% of the infections. *Staphylococcus aureus* was second most common and was reported to cause 23.8% of the infections [7]. The virulence of the infective organisms can affect the course of treatment, but the age of the patient appears to have some bearing on the outcome and the number of arthroscopic procedures required to control the infection. Mouzopoulos et al. reported that patients over the age of 25 years required, on average, 1.12 more procedures to control infection compared to patients under the age of 25 [9].

Immediate arthroscopic lavage and debridement should be followed by six to eight weeks of intravenous antibiotic therapy, and then two to four weeks of oral antibiotics. In cases of persistent infection, repeat arthroscopy is recommended, but serious consideration for graft removal should be considered [9]. In patients with a retained graft, McAllister et al. reported that an average of 2.75 procedures were needed to sterilize the knee joint [5]. Graft retention is important, as 30% of patients with the graft retained following surgery experienced knee instability compared to 65% of patients who had their graft removed [11,13]. Early diagnosis of infection is critical, as the literature has reported that infection diagnosed within seven days post-ACL reconstruction has a higher rate of graft salvage than those infections diagnosed beyond seven days post-op [7]. Furthermore, graft retention following infection after ACLR is a viable procedure with a reported overall success rate of 85% [14].

Upon reviewing the literature, it was found that at least two arthroscopic treatments are needed to control infection after ACLR and prior to graft and hardware removal. Despite the lack of randomized clinical trials, several retrospective studies have reported that arthroscopic lavage and debridement for infection following ACLR is an effective therapeutic intervention to minimize the severity of sequelae, including osteoarthritis, osteomyelitis and arthrofibrosis [5].

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QUESTION 6: How many arthroscopic procedures are reasonable for the management of an infected anterior cruciate ligament reconstruction (ACLR) prior to considering arthrotomy?

RECOMMENDATION: It is reasonable to treat acute infection of the knee following ACLR with arthroscopic debridement, repeating the arthroscopy up to six times, if necessary. The use of arthrotomy in the management of infected anterior cruciate ligament (ACL) cases is not well defined.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infection following ACLR is rare but can be a potentially devastating complication. However, if early appropriate surgical intervention is performed, the functional outcome may be comparable to non-infected cases of ACLR [1].

Historically, septic arthritis of the native knee was treated with open debridement and varying degrees of synovectomy, as described by Ballard et al. [2]. More recently, Riel et al. demonstrated arthroscopic irrigation and debridement with good results and since then, they have become a routine treatment option for an infected ACLR [3]. Several subsequent studies have described arthroscopic debridement as the initial treatment of choice for the management of septic arthritis of the knee [4].

Makhni et al. conducted a systematic review on functional outcomes following surgical treatment of the infected knee following ACLR. The studies included in the analysis demonstrated that up to six arthroscopic procedures were performed for the resolution of infection and symptoms [4].

Böstrom et al. examined outcomes following infected ACLRs. They described a standard treatment protocol of repeated arthroscopic debridements, with a mean of 3.7 procedures per patient, although the range was wide (1 to 11 procedures) in all patients [5]. Another systematic review by Saper et al. concluded that arthroscopic debridement with graft retention is an effective treatment of infection following ACLR. The mean number of arthroscopic procedures per patient in these studies was 1.5 (range, 1 to 4) [6].

Interestingly, Petersen et al. used a treatment approach according to the Gaechter classification system. In their study, they reported complete resolution of infection following ACLR in all patients without arthrotomy. For Gaechter stage I and II patients, the mean number of arthroscopic debridement's was 2.5, while in stage III patients it was 3.4. There were no stage IV patients reported [7]. Similarly, Gille et al. utilized a treatment algorithm based on the stage of infection according to Gaechter [8]. In patients with stage III or IV infections, medial and lateral arthrotomy with near total synovectomy was performed after initial arthroscopy.

Torres-Claramunt et al. reported mean of 1.3 (standard deviation = 0.6) arthroscopic debridements in their study, and one patient required three procedures. The authors recommended repeated arthroscopic debridement, usually after 48 to 72 hours, if clinical and laboratory parameters do not improve [9]. Abdel Aziz et al. examined 24 patients with an infected ACLR, who required between 1 and 6 arthroscopic debridements before achieving complete resolution of infection [10].

The literature on the number of arthroscopic procedures needed prior to arthrotomy for an infected ACLR is sparse. Nevertheless, studies have shown that repeated arthroscopic procedures can give good results, although the number of procedures required varies. As a consequence, there may be no need to treat an infected ACLR with arthrotomy in most cases. However, in more severe and neglected cases (Gaechter stage IV), arthrotomy should be considered after initial arthroscopic evaluation of the joint.

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QUESTION 7: What is the optimal duration of antibiotic treatment after surgical debridement of an infected anterior cruciate ligament reconstruction (ACLR)? Should this be altered when autograft or allograft is retained?

RECOMMENDATION: Following surgical debridement of an infected anterior cruciate ligament (ACL), antibiotic treatment should be administered for four to six weeks and can be discontinued upon resolution of clinical signs and normalization of laboratory parameters. The available literature does not differentiate between retention or removal of autograft or allograft.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

ACLR surgery is an anatomically complex procedure with high success rates and low infection rates [1–3]. Nevertheless, the onset of an infection after reconstructive ACL surgery is a devastating complication that can cause, in a short period of time, a progressive degeneration of the articular cartilage, graft failure and loss of function of the knee [1–3]. A prompt diagnosis and correct management might reduce or even prevent these unfavorable outcomes [4]. The incidence of infection following ACLR ranges from 0.14% to 1.8% [5–8].

Arthroscopic debridement followed by antibiotic treatment is the preferred therapeutic approach in aiming to control the infection and save the graft. Indeed, satisfactory functional outcomes are achieved in several cases of septic arthritis following ACLR with a graft salvage rate of about 85% [9]. However, persistent infection, despite multiple arthroscopic debridements, requires graft removal and subsequent ACL revision surgery at a later stage [9]. The duration and the route of administration of antibiotic therapy, in particular when to switch from intravenous (IV) to enteral administration, remain controversial [4].

Even though the duration of antibiotic treatment can vary between 4 and 14 weeks, most authors agree that it should be administered for no less than 6 weeks [4,10–12]. IV administration is preferable for the first two to three weeks [3,8,13]. However, the microorganism cultured and the antibiogram together with the postoperative clinical and laboratory parameters dictate the precise duration of antibiotic treatment [14].

In a systematic review, Wang et al. [15] evaluated 17 articles that fulfilled the inclusion criteria of septic arthritis following ACLR. The authors found that the arthroscopic debridement with graft retention and IV antibiotics was the treatment of choice for infected ACLR in most studies, with delayed diagnosis and treatment being the greatest risk factors for graft removal and articular cartilage damage. Indeed, out of 176 patients included in all the studies, 86.9% (153/175) underwent arthroscopic debridement for septic arthritis. IV antibiotics were continued for an average period of 29.7 days [15]. IV antibiotics for an average of four to six weeks was recommended, which might then be changed to oral antibiotics as soon as the C-reactive protein (CRP) levels drop to nearly normal values (< 1 mg/mL) [3,10,11]. Oral antibiotics were then administrated for at least another 14 days until the CRP returned to normal [15].

Out of 176 patients present in all studies, 18.75% (33/175) underwent graft removal, but the optimal duration of antibiotic treatment was not clearly reported. In two studies, the revision surgery was performed 12 months or later after the infection had resolved [16,17]. However, in another study by Burks et al. the revision ACLR was performed within six weeks after the completion of the antibiotic therapy and after the laboratory values had returned to normal [18].

Mouzopoulos et al. [19] proposed the basic management protocol with graft retention based on IV antibiotic therapy over at least four weeks followed by oral antibiotic for two to four weeks. An extended IV antibiotic therapy was given only in patients who needed more arthroscopic lavages. However, the therapeutic management in case of graft removal or retention is not well distinguished.

Gobbi et al. [20] stated that serial arthroscopic lavages and IV antibiotics with graft retention remain the most effective treatment protocol, starting with empirical therapy at the time of presentation. IV antibiotics switch to culture-sensitive oral antibiotics as soon as the CRP levels have nearly normalized (< 1 mg/mL) for six weeks, or until normalization of clinical and laboratory parameters. The average duration of IV antibiotics ranges from 17.3 days to six weeks, followed by oral administration for up to 3.2 months [2,3,7,8,11,13,21–23].

Shuster et al. [24] created a detailed treatment algorithm in which the graft is preserved as long as possible. However, graft removal is considered in persistent infections after multiple revisions, in loosened fixation or in graft insufficiency. In patients undergoing debridement and irrigation, a chain of antibiotic (gentamicin) loaded beads was inserted, protruding through the wound to allow stepwise removal within approximately one week. Empiric antibiotic therapy (cephalosporin I or II combined with an aminoglycoside, clindamycin or rifampicin) is started and antibiotic treatment is re-evaluated every day and changed according to microbiological testing, if necessary. When patients show clinical

improvement over five to six days with consistent and substantial decreases in CRP levels, they are discharged with oral therapy and weekly follow-up examinations. The duration of antibiotic therapy is based on the individual course of each patient and antibiotic therapy is terminated when CRP levels are within normal range (< 5 mg/L) [25]. The mean duration of inpatient treatment was 16.5 ± 8.2 days (range, 4 to 45 days). The mean duration of antibiotic treatment was 5.4 ± 2.3 weeks (range, 2.1 to 12.9 weeks). In 13 patients (36%), the duration of antibiotic treatment was < 4 weeks. A maximum of two arthroscopic irrigation and debridement procedures (mean, 1.46 ± 0.52) was necessary for eradication of the infection in these patients [25].

The available evidence does not allow for drawing a conclusive recommendation regarding the optimal duration of antibiotic treatment after surgical debridement for infected ACLR. However, the literature suggests that antibiotic treatment should be followed for four to six weeks and continued until clinical conditions are improved. Moreover, the literature is still controversial on the duration of antibiotic treatment in case of graft and hardware retention or removal, focusing mainly on the former case. Furthermore, most of the authors do not differentiate between autograft and allograft, considering and treating them in the same manner.

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QUESTION 8: Should the rehabilitation protocol be modified after surgical debridement of an infected anterior cruciate ligament reconstruction (ACLR)? If yes, what changes should be made with regards to range of motion and weightbearing status?

RECOMMENDATION: We recommend that rehabilitative treatment after surgical debridement of an infected ACLR with graft retention should not differ substantially from primary reconstruction; it should be focused on preventing stiffness and regaining motion through passive and active-assisted range of motion exercises before progressing.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The development of an infection after ACLR can have significant complications including loss of articular cartilage, graft failure and loss of knee function [1–3]. Although there is wide agreement that treatment must be initiated as early as possible, several different treatment algorithms have been proposed [4–7]. With regards to the postoperative treatment, there are no studies directly focusing on rehabilitation protocols.

While it is well-established that a graded knee-strengthening program (including quadriceps and hamstrings strengthening) has to be started within the first postoperative days [4,8–11], there is no agreement regarding weightbearing status and range of motion parameters.

Rehabilitative treatment after surgical debridement of an infected ACLR does not differ substantially from primary reconstruction. It should be focused on preventing stiffness and regaining motion through passive and active-assisted range of motion exercises.

There are no studies suggesting an altered rehabilitation protocol in the setting of a postoperative infection. Monaco et al. [10] suggest the use of a brace locked in extension for two weeks, followed by a progressive increase in the range of movement and muscular strength. Alternatively, many authors allow immediate full range of movement under the supervision of a physical therapist [7,11]. Indelli et al. [12] and Wang et al. [3] recommend starting rehabilitation only after complete resolution of symptoms, and suggest only passive motion of the knee and the ankle in the meantime.

There is a lack of consensus on weightbearing status after treatment of an ACL infection. Torres-Claramunt et al. [4,13] suggest starting a strengthening program two weeks after surgery with progressive weightbearing after symptoms decrease. Likewise, weightbearing was gradually increased until resolution of symptoms in the rehabilitation protocol developed by Hantes et al. [14]. However, McAllister et al. [15] and Schub et al. [16], suggest beginning the weightbearing six weeks after surgery.

Overall, there is a lack of evidence to support a standardized approach to rehabilitation after the surgical debridement of an infected ACLR. High-quality controlled trials are needed to provide guidelines for this rare and difficult complication.

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QUESTION 9: When can patients safely undergo revision anterior cruciate ligament reconstruction (ACLR) following treatment for prior infection?

RECOMMENDATION: It is considered safe to perform a revision ACLR following completion of successful treatment for infection and normalization of clinical and laboratory parameters upon resolution of the infection. The literature does not suggest a specific timeframe following resolution of the infection prior to performing revision ACLR.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 92%, Disagree: 0%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

Infection following ACLR is rare, with a reported incidence of 0.14% to 2.25% [1,2]. When infection does occur, there are potentially significant consequences, particularly regarding patient outcomes [3]. Following allograft ACLR, there is a well-known risk of disease

transmission, although a recent literature review found no difference in infection rates between autograft and allograft ACL reconstructions [4,5].

Graft retention following an infected ACLR is a viable option, as a recent meta-analysis and systematic review reported a success rate of 85% [2]. Matava et al. surveyed 61 orthopaedic surgeons and found that graft removal was not popular as the initial treatment, with only 6% and 33% of respondents removing the autograft and allograft following ACLR infection, respectively. However, in cases of persistent infection, 36% of surgeons removed the graft as part of their treatment regimen [6]. The same survey showed that the most common time frame for revision surgery was a minimum of 6 to 9 months (range, 3 to 15 months) after eradication of the infection [6].

Despite successful outcomes with graft retention, graft removal and revision ACLR remains the preferred method for some surgeons following infection [7]. In a retrospective review, Burks et al. reported on 8 infections out of 1,918 ACL reconstructions. Seven of these were treated with immediate irrigation and debridement with subsequent graft removal and administration of intravenous antibiotics for six weeks. Of those, four successfully underwent revision ACLR at a mean of three weeks (range one to six weeks) after completing antibiotic treatment [7]. In another systematic review and expected value decision analysis of 19 studies, revision ACLR, within 3 to 6 weeks after the infection, was shown to have promising results [8]. Gille et al. prospectively studied 31 patients with ACL infection where the graft was salvaged in 8 patients (26 %) and removed in 12 patients (39 %). Only two patients underwent revision ACLR at six and eight months post infection [9].

Williams et al. reported on 2,500 ACLRs with 7 infections: the graft was removed in 4 cases. One of these cases underwent successful revision ACLR one year later [10]. In a retrospective review of 3,500 ACL reconstructions, Indelli et al. identified 6 infections treated with arthroscopic debridement of which 2 grafts were removed, culminating in 1 revision ACLR and 1 total knee arthroplasty (TKA) a year later [11]. Furthermore, another study reported one patient treated with initial graft removal and successful revision ACL surgery one year after treatment [12]. Zalavras et al. also described a series of five infected ACL reconstructions treated with radical debridement and graft removal. Two patients had further procedures: 1 revision ACL reconstruction 14 months later and 1 TKA nine months later [13].

Hantes et al. reported 7 infected cases in a series of 1,242 ACL reconstructions. One patient did well with irrigation and debridement and six had a recurrence of infection, requiring subsequent graft and hardware removal. These patients were offered subsequent revision ACLR and graft reimplantation three months after the last operation. Four of the six patients underwent revision with ipsilateral bone patellar tendon bone autograft at an average of five months (range four to nine) post eradication of infection. The authors recommend revision ACLR after eradication of the infection for at least three months, with normal knee motion, no knee effusion and normal laboratory values [14].

Despite the lack of randomized clinical trials, there are several retrospective studies with low numbers of revision ACLR following treatment for prior infection. There is no consensus on the appropriate timing of revision reconstruction, with a reported range of three weeks to over a year. In general, it seems appropriate to delay surgery for a minimum of six weeks, but waiting three to six months post-eradication of infection may be optimal. Importantly, criteria such as normal knee motion, lack of knee effusion and normal laboratory markers must be considered before proceeding.

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PART VII

ONCOLOGY

Prevention

1.1. PREVENTION: ANTIBIOTIC PROPHYLAXIS

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QUESTION 1: Is there a correlation between operative time and the risk of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI) in patients undergoing tumor resection and endoprosthetic reconstruction? If so, should postoperative antibiotics be prolonged in these patients?

RECOMMENDATION: Based largely on the arthroplasty literature, there is considerable evidence that prolonged operative time is associated with an increased risk for postoperative infection. However, there is insufficient evidence to suggest that a prolonged postoperative antibiotic regimen can mitigate this risk. Therefore, there is no evidence to support prolonged postoperative antibiotics in orthopaedic oncology patients undergoing surgeries of prolonged duration. If the duration of the procedure exceeds two half-lives of the prophylactic antimicrobial, intraoperative redosing is needed to ensure adequate serum and tissue concentrations of the antimicrobial.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A thorough literature search was conducted using PubMed, Google Scholar and the Cochrane database. Search terms included "infection," "surgical duration," "surgical time," "operative duration," "orthopaedic," "resection," "reconstruction," "endoprosthesis," "antibiotic duration" and "postoperative antibiotic" in various combinations. The majority of articles found did not specifically focus on orthopaedic oncology patients.

Several studies support the hypothesis that prolonged surgical time was associated with increased risk of postoperative SSI. In a systematic review conducted by Cheng et al. [1], 4343 studies initially identified were narrowed down to 81, many of which demonstrated nearly double the infection risk in cases that exceeded cutoff times of 1-4 hours, and almost threefold the risk in surgeries exceeding 5 hours. When all included studies were pooled, the authors observed the risk of SSI to increase by 5% for every 10 minutes of surgery, 13% for every 15 minutes, 17% for every 30 minutes, and 37% for every 60 minutes. Based on the seven orthopaedic-specific studies included in their review, they found a statistically significant association between operative duration and infection with an 84% increased likelihood of SSI when operative time exceeded different cut-off points ($p = 0.0003$).

In the arthroplasty literature, although some articles have demonstrated an association between prolonged operative time and increased risk of postoperative infection, it remains controversial whether increased operative time is an independent risk for SSI/PJI. Previous studies using administrative or registry databases have linked increased operative time to periprosthetic infection after total joint arthroplasty (TJA) with statistical significance [2–6]. However, the findings of these studies were limited by the significant heterogeneity of their samples and varying definitions for PJI as well as the definitions for operative time. Using data from a single institution, Peersman et al. [7] observed the risk of infection to increase significantly in total knee arthroplasty if the surgery took longer than 2.5 hours. They also investigated the impact of 24 vs. 48 hours of postoperative antibiotics on mitigating this increased risk and found no difference in the two antibiotic regimens. An epidemiological study of over 2,000 patients who underwent orthopaedic surgery in China also demonstrated that surgical time longer than three hours was an independent risk factor for development of SSI, with an odds ratio of 3.633 [8]. Pulido et al. corroborate these findings, showing that on univariate analysis longer operative time had statistically significant association with periprosthetic infection in 9,245 hip and knee replacement patients, but multivariate analysis adjusted for confounding factors revealed that operative time was not an independent predisposing factor for PJI [9]. In contrast, there are studies that failed to demonstrate such a correlation and even found an inverse relationship between operative time and PJI [10–14].

In the orthopaedic oncology patient, risks are even higher considering that patients are often immunocompromised and tumor resection can create a large dead space contributing to development of infection. The overall incidence of SSI in cases of malignant musculoskeletal tumors is reported as greater than 12% in some studies [15] and approximately 10% according to a large systematic review and meta-analysis [16]. Nagano et al. [15] demonstrated in their series of 457 patients with benign or malignant musculoskeletal tumors that duration of surgery is a significant risk factor in acquiring SSI (using threshold of 355 minutes), with an odds ratio of 6.06. Li et al. [17] reviewed a series of 53 patients with osteogenic sarcoma who underwent resection and segmental replacement, demonstrating a postoperative infection rate of 7.5%, much higher than primary arthroplasty. They utilized an antibiotic regimen consisting of three days of intravenous antibiotics followed by five days of oral antibiotics for all of the patients, and the authors were unsure whether this made a meaningful difference. In patients undergoing allograft reconstructions, the infection rate is also high: Tann and Mankin demonstrated a 9% infection rate in their series with the duration of the operative procedure to significantly increase the infection rate [18].

Surgeons have attempted to mitigate infection rates in high-risk patients by administering postoperative antibiotics for a prolonged period; largely, the efficacy of this strategy is not borne out in the literature. Aponte-Tinao et al. [19] report an overall infection rate of 9% in their series of 673 patients who underwent massive allograft reconstruction after tumor resection. Interestingly, a longer period of postoperative antibiotics was found to be a risk factor in development of infection. In the arthroplasty literature, there has also been no benefit associated with prolonged postoperative antibiotic use: Nelson et al. [20] argue that the optimal duration of antibiotics after surgery is 24 hours, as the risk of SSI did not decrease in their randomized controlled trial comparing that to a 7-day regimen. International Consensus Meeting on Periprosthetic Infections in 2013 recommended the use of 1 dose preoperatively and 24 hours of coverage postoperatively [21]. Although the Centers for Disease Control and Prevention recently released their 2017 Guideline for the Prevention of Surgical Site Infection [22], which recommends against the use of postoperative prophylactic antibiotics, including patients undergoing total joint arthroplasty, the American Association of Hip and Knee Surgeons (AAHKS) does not agree with this recommendation [23]. At this time, the AAHKS recommends postoperative antibiotics be continued for 24 hours and supports further research to determine whether shorter duration antibiotic treatment is safe and effective. Both the Board of Counselors and Board of Specialty Societies of the AAOS have endorsed this AAHKS recommendation through an advisory opinion; the American Academy of Orthopaedic Surgeons' Board of Directors adopted that advisory opinion in June 2017 [23]. In their comprehensive publication of clinical practice guidelines for antimicrobial prophylaxis in surgery, Bratzler et al. [24] recognize that duration of surgery is a risk factor for SSI but maintain the recommendation that the duration of postoperative antibiotics for orthopaedic procedures should be less than 24 hours. In cardiothoracic procedures in particular, the exception is made for a recommendation of up to 48 hours. Orthopaedic oncology patients undergoing prolonged surgical resection and reconstruction are not listed as an exception, despite their increased risks as outlined above. An ongoing large international randomized controlled trial, the Prophylactic Antibiotic Regimens in Tumor Surgery (PARITY) has published its feasibility pilot [25] and is scheduled to complete enrolment of 600 patients by the end of 2019 (NCT01479283). The study will determine if five days of postoperative antibiotics reduces infection rates compared to one day of postoperative antibiotics in the orthopaedic oncology population.

Although a longer period of postoperative antibiotics is not recommended by the guidelines [22–24], intraoperative redosing is needed to ensure adequate serum and tissue concentrations of the antimicrobial if the duration of the procedure exceeds two half-lives of the antimicrobial or there is excessive blood loss (i.e., > 1,500 mL). The redosing interval should be measured from the time of administration of the preoperative dose, not from the beginning of the procedure.

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QUESTION 2: Should factors like preoperative radiation, soft tissue vs. bone resection, presence of metal vs. structural allograft and other factors influence the dose and duration of antibiotic prophylaxis?

RECOMMENDATION: Unknown. Evidence and guidelines directing the prescription of prophylactic antibiotic regimens in musculoskeletal tumor surgery are lacking. Although long-term antibiotic prophylaxis may decrease the risk of deep infection, there is not sufficient evidence to recommend the use of anything other than routine antibiotic prophylaxis for patients undergoing major reconstruction.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Limb salvage and reconstruction using endoprostheses or bulk bone allografts have become standard of care for the management of bone tumors. In order to minimize peri- and postoperative risk for periprosthetic joint infection (PJI) development, antibiotic prophylaxis is routinely administered. While standard guidelines for primary total joint replacements exist and are widely accepted, there are no such guidelines/recommendations for reconstruction using endoprostheses or bulk bone allografts in orthopaedic tumor surgery. As a result, various opinions and variations exist between surgeons on the prescription of prophylactic antibiotic regimens in tumor surgery [1].

Duration of antibiotic prophylaxis remains one of the most important issues. For primary total joint replacement, consensus exists in that, postoperative antibiotics should not be administered for greater than 24 hours after surgery. However, oncologic patients represent a heterogeneous population which significantly differs from population of patients that undergo primary joint replacement, and different antibiotic regimes may be necessary.

There is considerable variation in the antibiotic regimens reported by available studies. Only seven studies specified the dose (i.e., 1 gm) and/or the type of prophylactic antibiotics administered (i.e., first-, second-, or third-generation gram-positive cephalosporin) [2–8]. Two studies specified giving additional coverage against gram-negative bacteria as well [5,6]. Twenty studies reported postoperative antibiotic regimens. These studies were subdivided into short-term regimens (0 to 24 hours of postoperative antibiotics) [2,3,7,9–12] and long-term regimens (greater than 24 hours of postoperative antibiotics) [4–6,8,13–21] and compared.

Several attempts were made in order to address this issue. A systematic review reported by Racano et al. (analyzing 4,838 patients included in 48 Level 4 studies) suggests that long-term antibiotic prophylaxis (pooled weighted infection rate 8%) is more effective than short-term prophylaxis (pooled weighted infection rate 13%) at minimizing infection in patients with lower extremity long-bone tumors that require surgery and endoprosthetic reconstruction [22]. Authors recognize limitations of the study, such as inconsistency in antibiotic prophylaxis used in each study, inconsistency in reporting applied regimens (only seven studies specified the dose and/or the type of antibiotics administered), majority were retrospective studies, and it was unclear whether the definition of infection is constant in all studies, since criteria changed over time [22]. These findings are important for two reasons. First, they support the notion that orthopaedic oncology patients are diverse populations who may require a diverse prophylactic regimen when compared to conventional arthroplasty patients. Second, these results reinforce the increasing need to limit infections and establish guidelines for antibiotic prophylaxis in tumor surgery.

In contrast, Aponte-Tinao concluded that prolonged periods of postoperative antibiotics were associated with a greater risk of infection. Other risk factors associated with increased infection rate were tibial allograft, male patients and procedures performed in conventional operating room [23].

Currently, there is an ongoing multicenter randomized controlled trial titled Prophylactic antibiotic regimens in tumor surgery (PARITY). This study includes a parallel two-arm design to investigate whether a 24-hour (short) or 5-day (long) antibiotic prophylaxis regimen should be implemented among patients undergoing surgical excision and endoprosthetic reconstruction of lower-extremity primary bone tumors [24]. The primary outcome is the rate of deep postoperative infections in each arm. Secondary outcomes include type and frequency of antibiotic-related adverse events, patient functional outcomes and quality-of-life scores, reoperation and mortality. Patients will be followed for one year after the procedure. The results of the final study are expected soon [25].

Unfortunately, there is insufficient literature to support alternate antibiotic regimens in patients who underwent preoperative radiation, patients who underwent soft tissue or bone resection, or patients who received a metal endoprosthesis or structural allograft after tumor resection. The main reason is poor reporting of the antibiotic regimens (dosage, duration, etc.), and therefore, all conclusions may be misleading. Even if this data were available, it would not be accurate to properly compare the infection rates of different clinical series based on their perioperative antibiotic protocols because of the heterogeneity of patient populations.

Since data on prophylactic antibiotic regimens are rather scarce, high quality, randomized controlled trials are needed for oncologic endoprosthesis or bulk bone allograft reconstructions in tumor orthopaedic surgery. As a result, the strength of the recommendation is limited.

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QUESTION 3: Should patients with an oncologic endoprosthesis in place receive antibiotic prophylaxis during dental procedures?

RECOMMENDATION: Not routinely. Evidence-based guidelines by dentists and orthopaedic surgeons state that antibiotic prophylaxis is rarely appropriate for patients with prosthetic joints.

LEVEL OF EVIDENCE: Consensus.

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The American Dental Association (ADA) [1] and the American Academy of Orthopaedic Surgeons (AAOS) [2,3] have issued updated guidelines regarding the need for antibiotic prophylaxis. The guidelines do not specifically address the topic of patients with an oncologic endoprosthesis. The guidelines are based on four case-control studies [4–7] that found no association between dental procedures and PJI and no effectiveness for antibiotic prophylaxis.

The ADA recommended that, "in general, for patients with prosthetic joint implants, prophylactic antibiotics are not recommended to prevent prosthetic joint infection." Likewise, the AAOS recommended that "the practitioner might consider discontinuing the practice of routinely prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants undergoing dental procedures." The AAOS recommendations were more conservative than the ADA recommendations. The AAOS conducted a study using a modified Delphi procedure in which 14 experts were given scenarios involving patients with prosthetic joints and voted whether antibiotic prophylaxis was appropriate. The panel concluded that prophylaxis may be warranted in the following situations: procedures involving manipulation of the gingival tissue or periapical region of teeth or perforation of the oral mucosa in patients who are severely immunocompromised and (1) have uncontrolled diabetes (glucose > 200 mg/dl, $HbA_1C > 8\%$), or (2) have controlled diabetes (glucose < 200 mg/dl, $HbA_1C < 8\%$) and have a history of periprosthetic joint infection (PJI) that required surgery or (3) do not have diabetes and have a history of PJI that required surgery and the initial joint replacement surgery was < 1 year ago.

The Dutch Orthopaedic and Dental Societies issued guidelines based on nine studies, all deemed to be very low quality. These guidelines advise that antibiotic prophylaxis should not be given to prevent PJI, regardless of the patient's immune status.

Given the absence of studies in patients with an oncologic endoprosthesis, it seems prudent to apply the more moderate AAOS guidelines to this patient population.

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QUESTION 4: Should prophylactic antibiotics be started in patients with an oncologic endoprosthesis who develop neutropenia secondary to postoperative chemotherapy?

RECOMMENDATION: Not routinely. Evidence-based guidelines recommend limiting the routine use of prophylactic antibiotics to high-risk patients with chemotherapy-induced neutropenia.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Guidelines published by the Infectious Diseases Society of America (IDSA) and the National Comprehensive Cancer Network (NCCN) recommend the use of fluoroquinolone prophylaxis during neutropenia in high-risk patients [1,2]. Risk stratification is based on a number of criteria, including malignancy type. According to IDSA guidelines, "Low-risk patients are those with neutropenia expected to resolve within 7 days and no active medical co-morbidity, as well as stable and adequate hepatic function and renal function. These low-risk features are most commonly found among patients with solid tumors" [1].

These recommendations are based on meta-analyses which included predominantly patients with hematological malignancy [3–5]. None of the articles included in the meta-analyses examined antibiotic prophylaxis in patients with primary bone malignancy or patients with an oncologic endoprosthesis. Furthermore, none of the articles specifically addressed cancer patients with foreign bodies. The largest and most comprehensive of the meta-analyses found that antibiotic prophylaxis reduces overall mortality versus placebo, with a number-needed-to-treat of 34 and low heterogeneity [4].

Two reasons limit the use of antibiotic prophylaxis in low-risk patients. First, concerns exist regarding the development of bacterial resistance and subsequent infection [2]. Although a meta-analysis found that fluoroquinolone prophylaxis leads to a non-significant increase in colonization with resistant bacteria with no difference in infections due to resistant bacteria, concerns remain [6]. Second, guidelines recommend treating low-risk patients with neutropenic fever as outpatients, with oral antibiotics including fluoroquinolones on an outpatient basis. It is unclear whether the potential benefit of prophylactic quinolone use is greater than that of the use of these agents as treatment [2,7]. In summary, given the evidence to date, patients with an oncologic endoprosthesis should not routinely receive antibiotic prophylaxis during neutropenic episodes.

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QUESTION 5: What type, dose and duration of prophylactic antibiotic(s) should be administered to patients undergoing oncologic endoprosthetic reconstruction who have received or will be receiving chemotherapy and/or radiation?

RECOMMENDATION: Antibiotic prophylaxis should be given in accordance with existing guidelines for standard arthroplasty surgery and other orthopaedic surgical procedures with foreign body placement.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 93%, Disagree: 0%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Studies examining the effect of chemotherapy and radiation on risk of postoperative infection in tumor patients have found an increased risk of surgical site infection (SSI) following radiation therapy (thoracic, head and neck, gynecological, breast malignancies) and chemotherapy (thoracic, head and neck, breast malignancies) [1,2]. No studies have been conducted to compare different prophylactic antibiotic regimens for patients who received radiation or chemotherapy prior to surgery; in a single randomized, controlled trial comparing prophylactic antibiotics with placebo in breast cancer patients, no significant difference was seen in the risk of developing postoperative infection between patients who received neoadjuvant chemotherapy and those who did not [3].

Studies examining the effect of chemotherapy and radiation on risk of postoperative infection specifically in patients with bone tumors and metastases have shown differing results based on the type and location of disease. A study of patients who underwent a variety of lower-extremity oncological operations did not find either chemotherapy or radiation to increase the risk of infection [4]. Similarly, in a cohort of patients undergoing surgery for primary bone tumor, mostly involving the lower limb, chemotherapy was not a risk factor for infection, nor was it in a group of patients who underwent endoprosthetic reconstruction for tumors around the knee [5,6]. On the other hand, a study of patients with spinal metastases found that postoperative radiation was associated with increased risk of infection [7].

As no studies have been conducted addressing the tailoring of antibiotic prophylaxis in oncologic patients undergoing tumor surgery pre- or post-radiation or chemotherapy, including endoprosthetic reconstruction, prophylaxis should be given in accordance with existing guidelines for arthroplasty and other orthopaedic surgical procedures with foreign body placement [1,8]. In the event of colonization with methicillin-resistant *Staphylococcus aureus*, the choice of intravenous antimicrobial prophylactic agent should be adjusted accordingly.

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QUESTION 6: Does the type, dose, and duration of antibiotic prophylaxis differ for patients undergoing oncologic endoprosthetic reconstruction compared to conventional total joint arthroplasty (TJA)?

RECOMMENDATION: No. There is no recommendation to adjust type, dose or duration of antibiotic prophylaxis in patients undergoing oncologic endoprosthetic reconstruction from that which is routinely administered in conventional TJA.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 93%, Disagree: 0%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Rates of infectious complications following knee and hip arthroplasty are generally less than 2% [1]. However, rates of infectious complications following lower-extremity limb salvage therapy with endoprostheses are approximately 10% [2]. The reason for this difference remains unclear, possibly due to systemic factors not directly related to the presence of localized malignancy [3].

Preoperative parenteral antibiotics have been demonstrated to reduce wound infections following TJA [4]. In a meta-analysis of antibiotic prophylaxis in TJA, which included 7 studies with 3,065 participants, the relative risk of infection was reduced by 81% compared to placebo [4]. None of the studies included in the meta-analysis or accompanying systematic review specifically addressed prophylaxis in patients undergoing orthopaedic endoprosthetic reconstruction.

Based on the preponderance of evidence, clinical guidelines recommend the use of perioperative parenteral antibiotics before TJA and other orthopaedic surgeries with foreign body placement [5,6]. No data exist regarding the tailoring of prophylaxis in oncologic patients with endoprosthetic reconstruction. Therefore, antibiotics should be given in accordance with accepted regimens.

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1.2. PREVENTION: CHEMOTHERAPY

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QUESTION 1: Do we need to evaluate the gut and skin microbiome of patients after chemotherapy to assess the risk for potential infection after endoprosthetic reconstruction?

RECOMMENDATION: Unknown. There is no evidence in the literature to suggest that evaluation of the gut and/or skin microbiome following chemotherapy aids with risk stratification for potential infection in patients undergoing endoprosthetic limb salvage surgery.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

In the orthopaedic oncology literature, infection rates following metallic endoprosthesis limb salvage surgery are high and vary from 2.2–34% [1–4]. In a systematic review of the literature, Henderson et al. found the overall rate of infection-related failure of endoprostheses to be 7.8% and infection as the most common mode of failure in their current investigation of primary endoprostheses. Proximal tibia replacements and total femur replacements were noted to be at particular risk, requiring infection-related revision surgery in 19.7% and 17.5% of cases, respectively [1].

While not fully understood or rigorously investigated, the causes of these high rates of infection are likely multi-factorial, including extensive surgical dissection and resection, increased operation time, substantial loss of blood, inadequate soft tissue coverage, implantation of large constructs with foreign material and, often in the case of oncology patients, a poor nutritional and compromised immune status [5].

Perioperative chemotherapy has been shown to increase the total revision rates of endoprosthetic reconstruction to 40% from 10% due to its reduction of osseointegration [6]. The impact of chemotherapy on the rates of infection following endoprosthetic reconstruction remains unclear. There are conflicting reports on whether immunological deficiency following chemotherapy is a risk for postoperative infection of endoprostheses. In a review, Kapoor and Thiyam documented that a compromised immune status after neoadjuvant chemotherapy may result in postsurgical infection having an increased infection rate of 20% [5]. While in a multicenter retrospective review, Morii et al. showed chemotherapy did not affect infection risk and suggested no drawbacks related to chemotherapy in regards to postoperative infection control of endoprostheses [2]. It was shown that some patients who developed infection during postoperative chemotherapy were controlled by amelioration of myelosuppression alone, while others required revision and antibiotic therapy [7].

Any measure that leads to decreased infection rates of metallic endoprosthesis reconstruction would be desirable. Given the prevalence of the problem and the severity of the consequences of deep infection, even weak evidence supporting a decrease in postoperative infection rates would be worth considering. While a few interven-

tions have been noted to be beneficial, as reported in retrospective case series, no rigorous, prospective studies have been completed in this population. In regard to the question above, there is no evidence (level I, II, III or IV) to support or reject evaluation of the skin or gut microbiome after neoadjuvant or adjuvant chemotherapy.

Conceptually, chemotherapy is known to alter the gut microbiome, which likely influences the development and manifestations of chemotherapy-associated mucositis [8–10]. When undergoing induction chemotherapy for acute myeloid leukemia, patients who developed infection after treatment were shown to have significantly lower baseline stool bacteria diversity and the therapy itself was shown to decrease microbiome diversity [11]. Taxonomic shifts in the gut biome have been demonstrated in lymphoma patients following chemotherapy, with decreases in Firmicutes (species including *Staphylococcus, Streptococcus, Enterococcus*) and Actinobacteria (*Streptomyces, Proprionibacteria*) and increases in Proteobacteria (*Escherichia, Salmonella, Vibrio, Helicobacter, Yersinia, Legionellales*) [8]. In a pediatric study of acute lymphoblastic leukemia (ALL), the abundance of Proteobacteria in the gut microbiome before chemotherapy was predictive of the infection risk and domination of the gut by *Enterococcaceae* or *Streptococcaceae* during current and subsequent phases of chemotherapy [12]. Decreased diversity in the taxa of the gut microbiome has been used as a predictive tool for chemotherapy-related bloodstream infection risk [13]. Chemotherapy alters the skin microbiome in that fungal infections are common during and following chemotherapy [14].

Despite these documented changes in the microbiome of the gut and on the skin and their relation to infection risk, there is no proven association or theoretical link with postoperative endoprosthetic infection. This is illustrated in two ways. First, the causative organisms of endoprosthetic infection are those typically found in postoperative periprosthetic joint infections (e.g., *Staphylococcus, Streptrococcus, Enterococcus,* Pseudomonas species) [2,7,15], which are not species noted to increase following chemotherapy (e.g., *Proteobacteria* and Fungi) [8]. Second, the average time to infection-related surgical revision of endoprostheses is 47 months following index endoprosthesis placement [1]. This timeline is long after chemotherapy has been completed and more than enough time for chemotherapy-induced changes in the diversity of the gut and skin microbiome to return to normal.

There is still a need for further research to clarify whether skin and gut microbiome testing would prove useful in risk stratification for infection following endoprosthetic reconstruction.

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QUESTION 2: Should an absolute neutrophil count of >1000/mm³ be the minimum for patients undergoing limb salvage surgery after receiving chemotherapy?

RECOMMENDATION: Yes. An absolute neutrophil count of >1000/mm³ should be the minimum for patients undergoing limb salvage surgery after receiving chemotherapy.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Neutropenia has been defined as an absolute neutrophil count (ANC) of 1500/mm³ or lower [1]. Historically, this cutoff value has been considered as a risk factor for developing infections and complications. Bodey et al. [2] initially described this association. They observed that the infection rate in patients with ANC below 1000/mm³ was 14% and below 100/mm³ up to 60% [2]. Furthermore, lower ANC levels have been identified as an independent risk factor for infections [3]. This latter publication also demonstrated that the

risk gradually increases as ANC decreases. In a more recent study, Lima et al. [4] evaluated patients with ANC levels less than or equal to 500 cells/mm³ further support this relationship.

Different chemotherapeutic agents are used in the treatment of bone and soft tissue sarcomas. Some have shown to be myelosuppressive and thus reduce the ANC [5]. This is also one of the most critical criteria to administering chemotherapeutic regimens as it has been directly associated with an increased risk of complications [3,6]. The combination of wide resection and neo-adjuvant/adjuvant chemotherapy is a standard treatment modality for bone sarcomas [7]. The combination of methotrexate (MTX), doxorubicin (ADR), cisplatin (CDDP) and ifosfamide (I) are agents used for conventional osteosarcoma [7–11]. For small round cell sarcoma including Ewing's sarcoma, multi-agent chemotherapy with vincristine-doxorubicin-cyclophosphamide, ifosfamide-etoposide (VDC-IE) is used [12,13]. Chemotherapy for high-grade non-round cell, soft tissue sarcoma is controversial, but the effectiveness of chemotherapy for such sarcomas has been shown in several studies [14–20]. The conventional key drugs for such condition include ADR and I [14,15,17]. In addition, dacarbazine (DTIC), gemcitabine (G) and docetaxel (D) became the options for soft tissue sarcomas [20–24]. Recent innovation in this area provided additional reagents including pazopanib, trabectedin and eribulin, which are mainly used as second line treatment for advanced soft tissue sarcomas [25–31].

When evaluating patients with low ANC undergoing surgical interventions, these patients also exhibit an increased risk of surgical site infection compared to patients with normal counts. Natour et al. [32] evaluated patients undergoing abdominal surgery in the setting of neutropenia. They categorized patients with ANC < 500/mm³, between 500/mm³ and 1000/mm³, and between 1000/mm³ and 1500/mm³. Patients with lower ANC also exhibited higher postoperative infection rates, hospital stay and mortality. A relatively recent study evaluated the risk for infection of implantable port devices in pediatric oncology patients [33]. Again, patients with low ANCs had higher infection rates compared to those with normal ANC.

No study was identified that directly associates infection risk in patients undergoing limb salvage and low ANC. Given that limb salvage surgery is a complex procedure, all efforts to avoid infection should be undertaken. Based on the available literature, we consider that patients with an ANC below 1000/mm³, either from the chemotherapy or the solid tumor itself, should not undergo limb salvage surgery until ANC is above 1000/mm³ and possibly above 1500/mm³.

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QUESTION 3: Should the serum white blood cell (WBC) count be taken into account prior to endoprosthetic reconstruction in patients who have undergone recent chemotherapy?

RECOMMENDATION: The association between chemotherapy and infection following endoprosthetic reconstruction remains controversial. However, in a multifactorial decision making process, there may be some benefit in accounting for the serum WBC count prior to endoprosthetic reconstruction.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infection continues to be one of the most serious complications after the reconstruction of an extremity using a tumor endoprosthesis. Past reports showed that the infection rate of a tumor endoprosthesis ranged from 4–36% [1–5]. The myelosuppressive properties of many chemotherapeutic drugs remain a theoretical risk for developing infection in these patients receiving a tumor endoprosthesis for an extremity tumor or metastatic lesions. However, this theoretical risk remains controversial. A handful of studies demonstrate a significant relationship between chemotherapy and periprosthetic infection in patients receiving an endoprosthetic device for an extremity tumor [3,6–9].

On the contrary, there are numerous studies that provide data supporting the idea that chemotherapy is not a significant risk factor for the development of periprosthetic joint infection (PJI) and surgical site infection (SSI) in these patients. Peel et al. [10] were able to demonstrate that chemotherapy, febrile neutropenia and bacteremia were not associated with the development of PJI. Jeys et al. [11] showed that there was no significant relationship between chemotherapy and the risk of infection. Biau et al. [12] reported that there was no significant difference in the rate of infection between patients who had received adjuvant treatment (including irradiation and chemotherapy) and those who had not received such treatment ($p = 0.13$). Finally, Meijer et al. [13] found no association between chemoradiation and increased rates of endoprosthetic infection.

Despite the conflicting evidence surrounding chemotherapy and the risk of endoprosthetic infection, there may be some benefit in taking into account the patient's serum WBC count prior to endoprosthetic reconstruction. It is widely known that lymphocytes play an essential role in combatting invading pathogens and facilitating wound healing after surgery [14]. In addition, Gulack et al. [15] reported that preoperative leukopenia prior to emergent abdominal surgery was a predictor for significant postoperative morbidity and mortality. However, they were not able to demonstrate a significant difference in the incidence of deep wound infection in patients with leukopenia vs. patients with a normal WBC count preoperatively ($p = 0.462$). These findings contrast with the work by Natour et al. [16], who noted that patients undergoing abdominal surgery with a preoperative absolute neutrophil count (ANC) less than 500 had significantly higher postoperative infection rates compared to patients who had a preoperative ANC between 500 and 1500. However, one must be cautious with the results from these studies, as they may not be generalizable to the particular patient cohort of focus.

Due to the fact that the literature doesn't show any significant differences between the infection rates between patients who are undergoing chemotherapy and those who are not receiving it, it makes sense to determine the WBC number as an additional diagnostic tool.

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QUESTION 4: What should be the time delay between preoperative chemo/radiotherapy and a surgical tumor resection in order to minimize incidence of surgical site infection/ periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: Unknown. There is no data that supports the best time delay between preoperative chemo/radiotherapy and a surgical tumor resection to minimize the incidence of SSI/PJI. There are multiple intrinsic factors of each patient that can determine the best time to implant an endoprosthesis after a neoadjuvant treatment. Although no significance was seen between preoperative radiotherapy and surgical timing on wound complications (WC), trends suggest rates are lower if surgery is performed between 3 and 6 weeks following radiotherapy.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

SSIs, PJIS and WCs can occur postoperatively with respect to musculoskeletal/orthopaedic related surgeries. The risk of these infections is more common when these surgeries are related to musculoskeletal tumor resections following established multimodal therapies of preoperative chemotherapy and/or radiotherapy [1,2]. SSIs are defined as infections occurring at the operative site that develop within 30 days of non-implant operation or 1 year in the case of implant (artificial material) based operations [3]. The incidence of SSIs following orthopaedic operations is 1–3% [4]. The incidence is expected to be much higher following surgery in malignant musculoskeletal tumors due to many patients' requiring preoperative/postoperative chemotherapy and/or radiotherapy. PJI after joint replacement surgery has been reported to occur in 1.55–2.5% of cases [5–7]. As with SSIs the incidence would be expected to be higher following tumor surgery. Wound complications rates have been shown to be higher in those receiving preoperative radiotherapy [6,8–10].

With respect to the timing of surgery after preoperative radiotherapy and/or chemotherapy, there is no established optimal timeframe for clinical practice. Decisions to date are made by clinician-team opinion. The effect of different timeframes on the development of SSI, PJI and WC rates in this group has not been extensively reviewed. We know that radiation impairs wound tissue repair though several mechanisms [11]. Ionizing radiation can damage fibroblasts leading to slow growth [12,13], dermal atrophy, necrosis and ultimately reduced wound strength [14–16]. As a result, in the initial period following radiotherapy, surgery is avoided and four weeks is thought to be required to allow for repopulation of normal tissues [17]. Acute systemic effects of chemotherapy are also well documented, including toxicity and immunosuppression. However, there is still no established timeframe with respect to when to surgically resect tumors post chemotherapy and this is guided by clinical assessment and clinician choice.

All seven included studies were retrospective case studies, four were single-center studies, while the other three were not specified. The total sample number of all seven studies combined was n = 1,585; sample sizes ranged from 18-798. Preoperative radiotherapy was used in five of the studies, preoperative chemotherapy in three.

SSI was statistically significant secondary to preoperative radiotherapy alone in three studies [19,21,23] and secondary to preoperative chemotherapy in two studies [21,22]. No statistical significance with respect to SSI and preoperative chemotherapy in one study [18]. The remaining two studies did not statistically assess SSI as an outcome measure [17,20]. Sugita et al., 2015, intended to study the effect of timing between radiotherapy and surgery on SSI; however, this was abandoned due to factors varying widely between cases [19].

None of the six included studies assess PJI as an outcome measure. There was no mention of PJIs being included in any other groups as a complication. Furthermore, no data on the effect of timing between radiotherapy and surgery on PJI was sourced.

One study showed statistical significance between neoadjuvant radiotherapy and postoperative infection, p = 0.008. This study did not classify specifically the type or location of these infections [23].

In terms of WC two of the studies assessed their association with preoperative treatment. Both studies looked at the effect of preoperative radiotherapy. Keam et al. (n = 165) investigated the effect of preoperative radiotherapy on WCs and no statistical difference was evident with univariate analysis (p = 0.11) [20]. This study also looked at the timing effect of < 30 (n – not specified) days and ≥ 30 days (n – not specified) between radiotherapy and surgery on WC rates. There was no statistical significance between these two timeframes (p = 0.59) [20]. Griffin et al., investigated the dichotomous effect of the time intervals of 3, 4, 5 and 6 between preoperative radiotherapy and surgery. The rate of wound complications was the primary outcome measure. When comparing ≤ 3 and > 3 weeks, WC rates were 15/39 (38%) and 227/759 (30%) respectively, p = 0.3. Comparing ≤ 4 and > 4 weeks, WC rates were 39/129 (30%) and 203/669 (30%) respectively, p = 1. Comparing ≤ 5 and 5 weeks, WC rates were 88/295 (30%) and 154/503 (31%) respectively, p = 0.8. Comparing ≤ 6 and 6 weeks, WC rates were 133/479 (28%) and 109/322 (34%) respectively, p = 0.08. At time points < 3 and ≥ 6 weeks, it is evident that

TABLE 1. Data extraction from included studies

Author	Study Type	Neoadjuvant Treatment	Time Between Treatment and Surgery	n	Postoperative Outcome
Miwa et al., 2017 [18]	Single-centre Retrospective	Chemotherapy	Not specified	108	Deep SSI 16/108 significant with univariate analysis ($p < 0.001$), not significant in multivariate analysis ($p = 0.156$)
Sugita et al., 2015 [19]	Non-specified Retrospective	Radiotherapy	Intention to analysis effect of timing *Abandoned	41	SSI 27/41 significant with univariate analysis ($p = 0.03$)
Griffin et al., 2015 [17]	Non-specified Retrospective	Radiotherapy	≤ 3, > 3 weeks ≤ 4, > 4 weeks ≤ 5, > 5 weeks ≤ 6, > 6 weeks	39, 759 129, 669 295, 503 476, 322 Total n = 798	WC 15/39 (38%), 227/759 (30%), $p = 0.3$ WC 39/129 (30%), 203/669 (30%), $p = 1$ WC 88/295(30%), 154/503 (31%), $p = 0.8$ WC 133/479 (28%), 109/322 (34%), $p = 0.08$ Overall WC 186/798 (23.3%) incidence SSI 56/798 (7%) incidence, *effect of time not studied
Keam et al., 2014 [20]	Single-center Retrospective	Radiotherapy	> 30 days ≤ 30 days	165	No difference between effect of preoperative radiotherapy > 30 and ≤ 30 days from surgery on wound complications ($p = 0.59$) No significant effect on WC with univariate analysis ($p = 0.11$)
Gradl et al., 2014 [21]	Single-centrer Retrospective	Radiotherapy Chemotherapy	Immediate Not specified	262 137 Total n = 399	SSI 50/153, significant with bivariate analysis ($p < 0.0001$) SSI 22/153, significant with bivariate analysis ($p = 0.02$)
Nagano et al., 2014 [22]	Single-center Retrospective	Chemotherapy	Not specified	18	SSI 6/18, significant with bivariate analysis ($p = 0.03$)
Behnke et al., 2014 [23]	Non-specified Retrospective	Radiotherapy	Not specified	56	Postoperative infection (Location/type not specified) in those with radiotherapy 14/56 (25%) when compared to those without 37/340 (11%), statistically significant, $p = 0.008$

there is a higher rate of WC (34-38%) when compared to 3-6 weeks (28-31%); however, statistically there is no difference between time points [17]. This trend, although not significant, may support the general avoidance of aiming for surgery too early or too late based on radiation induced local changes to tissue and skin. A large multi-center study may show more of an effect at these timeframes. This trend may be considered applicable to SSI/PJIs due to WC risk factors being theoretically close in nature to infection risk, particularly the local and systemic toxicities and effects of radiotherapy and chemotherapy respectively.

We identified seven relevant articles assessing the effect of preoperative treatment on SSI, PJI and WC with respect to musculoskeletal tumour resection. Results are highly variable between the studies and overall there is limited evidence of significance in results. SSI rates were significantly increased in 3/3 (100%) of studies that looked at preoperative radiotherapy and 2/3 (67%) of the studies that looked at preoperative chemotherapy. These are single center/non-specified studies; to further delineate results, larger multi-centre studies in the future are warranted. No effect on timing of preoperative treatment and surgery was observed with respect to SSI rates. Given that there is conflicting evidence between the effect of preoperative tumour treatment and SSI development, investigation into the effect of timing becomes difficult. However, as some studies have established positive association and the near future possibility of larger multi-center study results coming to fruition, it will be now be imperative to also investigate and study the effects of surgical timing post radio/chemotherapy on rates of SSI. No studies assessed periprosthetic joint infection specifically as an outcome. This may be due to PJI presenting as a rare outcome secondary to surgical tumour resection. Also, these infections may be included in another complication section of such studies. None of the studies included in this review have mentioned this as an observed complication. Therefore, more investigation and study is needed with respect to understanding the role of preoperative tumour management and surgical timing on the rates PJI.

In summary, there is strong evidence supporting the association between preoperative radiotherapy/chemotherapy and postoperative SSIs. There is no data on the association of preoperative treatment with respect to PJI rates. One study showed no association between preoperative radiotherapy and WC. There were two studies showing no significant difference between surgical timing post radiotherapy/chemotherapy with respect to wound complications; however, there was a trend towards higher wound complications rates in ≤ 3 weeks and > 6 weeks. More large-scale, well-designed

multi-center studies are required to more accurately assess the effect of timing between preoperative radiotherapy/chemotherapy and surgery on the rate of postoperative SSIs, PJIs and WCs.

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QUESTION 5: What strategies should be implemented to minimize the risk of surgical site infection/periprosthetic joint infection (SSI/PJI) in patients who have received chemotherapy or radiation therapy and are undergoing endoprosthetic reconstruction?

RECOMMENDATION: We believe patients who have received either chemotherapy or radiotherapy prior to endoprosthetic reconstruction should undergo extensive medical optimization. Consideration may also be given to the use of antimicrobial coated implants, extended (>24 h) and augmented postoperative antibiotic prophylaxis consisting of a first-generation cephalosporin and an aminoglycoside and/or vancomycin, as well as use of enhanced soft tissue reconstruction techniques. Surgery should also be expeditious in these patients minimizing dissection of soft tissues with gentle handling.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Patients with neoplasia undergoing endoprosthetic reconstruction are at an increased risk of SSI/PJI. The chemotherapy-induced immunosuppression, the poor soft-tissue conditions due to radiotherapy, the length and complexity of the tumor resection and megaprosthetic reconstruction and the difficulty of achieving soft tissue coverage are some of the reasons that explain the very high rate of infection in these patients compared to patients undergoing conventional arthroplasty [1–5].

As these patients are at high risk of SSI and/or PJI, any measure proven to be effective against infection should be implemented. Several organizations have proposed evidence-based guidelines for the prevention of surgical site infections. These strategies, together with additional measures, should be implemented in these patients. We provide examples of some of the measures that may be used to minimize the risk of SSI/PJI in patients undergoing oncologic endoprosthetic joint reconstruction, particularly in patients who have received chemotherapy and/or irradiation treatment. These measures include:

- Preoperative measures [6–9]: Correction of hyperglycemia, treatment of anemia, treatment of malnutrition, smoking cessation, decolonization of *Staphylococcus aureus* (including methicillin-resistant *S. aureus* (MRSA)), skin cleansing with chlorhexidine or other antiseptic agents prior to surgery and numerous other preoperative measures that are discussed elsewhere in the consensus document should be considered.

- Intraoperative measures [6–9]: Administration of weight-based antibiotics, including coverage against MRSA if present, re-dosing of the prophylactic antibiotic for cases that last longer than two hours or have increased blood loss, minimizing blood loss by administration of tranaxemic acid, minimizing operating room traffic, use of antibiotic-impregnated bone cement, wound irrigation with antiseptic agents such as sterile dilute betadine, careful and gentle soft tissue dissection and expeditious surgery are some of the proven strategies that may be implemented intraoperatively.
- Postoperative measures [6–9]: Wound management is a critical aspect of prevention of SSI/PJI in these patients. Consideration should be given to administration of less potent anticoagulation to minimize hematoma formation or reduce the chance for persistent wound drainage. The incision may be managed by application of negative pressure or occlusive dressing. Every effort should also be made to minimize blood loss and the need for allogeneic blood transfusion.

There are many other preventative measures that have been proposed or explored in oncologic patient population undergoing megaprosthetic reconstruction. In recent years the use of implants coated with antimicrobial agents such as silver and iodine has been explored. Silver-coated prostheses for limb reconstruction after tumor resection has been reported to have a favorable outcome and be effective in reduction of infection. Among the metals known to have antimicrobial activity, silver has attracted interest among many investigators due to its excellent level of antimicrobial activity and low toxicity. The silver coating can inhibit bacterial colonization of the prosthetic body and potentially prevent subsequent PJI [10–12]. A study involving patients with bone sarcoma over a five-year period demonstrated that the infection rate was substantially reduced from 17.6% in the uncoated titanium megaprosthesis (proximal femur, n = 33; proximal tibia, n = 41) to 5.9% in the silver-coated megaprosthesis group (proximal femur, n = 22; proximal tibia, n = 29). The titanium group data were retrospective and the data for the silver group were collected prospectively [13]. Another study evaluating the infection rate in 98 patients with sarcoma or giant-cell tumor in the proximal tibia demonstrated that infection at 16.7% in the group who underwent reconstruction using titanium megaprostheses (n = 42) was significantly higher than the infection rate at 8.9% in the silver-coated megaprostheses group, resulting in five-year prosthesis survival rates of 90% in the silver-coated and 84% in the titanium only cohort. Although not reaching statistical significance, further work may suggest that silver-coated tumor prostheses may reduce the PJI rate in the high-risk oncological patients submitted to tumor resection and limb reconstruction.

Another study retrospectively investigated 68 oncology patients, 30 of whom received a titanium proximal femoral replacement and 38 patients who received a silver-coated proximal femur replacement. There was a lower rate of early infections (within the first 6 months) in the silver-coated group (2.6%) in comparison with 10% in the titanium group. However, the difference was not statistically significant. Regarding late-onset infections (later than 6 months), the difference between groups was not clear (5.3% in the silver group and 6.6% in the titanium group) [14]. The reports available on the use of silver-impregnated implants are all retrospective with their inherent limitations. The role of silver coating of megaprostheses in prevention of infection needs to be explored in a prospective manner.

Currently, there are no appropriate guidelines or recommendations in place for prophylactic antibiotics in patients with neoplasm undergoing endoprosthetic reconstruction. Although the beneficial role of perioperative antibiotic prophylaxis is proven, it is not known whether continuation of antibiotics beyond the traditional 24 hours is beneficial. Further, there is no consensus among the experts on the type of antibiotic prophylaxis that may be needed in tumor surgery patients with great variation between centers. Although most surgeons provide gram-positive coverage, others also provide gram-negative coverage. In addition, the length of administration of postoperative antibiotics has varied vastly [2,15]. A cross-sectional international survey of practicing orthopaedic oncology surgeons found that 73% (95% confidence interval (CI) 61, 82%) of respondents prescribe a first-generation cephalosporin, 25% favor additional coverage with an aminoglycoside (gentamycin) and/or vancomycin or teicoplanin. Of those who prescribe a cephalosporin, 33% prescribe a dosage of one gram for all patients and the remainder prescribe up to 2 grams based on the body weight. One in three surgeons (95% CI: 25, 48%) believe antibiotics could be discontinued after 24 hours, but 40% of surgeons (95% CI: 30, 53%) continue antibiotics until the suction drain is removed.

In higher-risk cases of tumor patients who have received chemotherapy and/or irradiation, no guidelines exist to direct antibiotic management. It is a common practice to continue the antibiotics beyond 24 hours in these patients. There is no prospective study that has examined the efficacy of different antibiotic regimens in preventing infection in long-bone prosthetic reconstruction [15].

Studies comparing single-dose prophylaxis and multiple-dose prophylaxis in a general surgery setting have not shown any benefit to extended course of antibiotics [16]. A systematic review involving 48 studies on a total of 4,838 patients (level IV retrospective studies) suggests that long-term (greater than 24 hours) postoperative antibiotic prophylaxis is more effective at minimizing infection risk in patients with lower extremity long-bone tumors that require surgery and endoprosthetic reconstruction. However, the data should be interpreted with caution owing to the retrospective nature of the included studies. The overall pooled weighted infection rate for lower-extremity limb salvage surgery with endoprosthetic reconstruction was approximately 10% (95% CI: 8%–11%), with the most common causative organism reported to be gram-positive bacteria in the majority of cases. Twenty studies reported postoperative antibiotic regimens, so they were further subdivided into short-term regimens (0 to 24 hours of postoperative antibiotics) and long-term regimens (greater than 24 hours of postoperative antibiotics) and compared. The pooled infection rate following short-term postoperative antibiotic prophylaxis was 13% (95% CI: 9% to 17%; $p < 0.001$), which is slightly higher than the overall pooled infection rate. The pooled infection rate for the long-term postoperative antibiotic prophylaxis was 8% (95% CI: 6% to 12%; $p < 0.05$), which is slightly lower than the overall pooled infection rate. This difference in the pooled infection rates following short-term and long-term postoperative antibiotics was statistically significant ($p < 0.05$) [2].

There is no dispute to suggest that tumor patients undergoing endoprosthetic reconstruction are at higher risk of infection than those undergoing conventional joint arthroplasty. The risk of infection is further increased in patients who have received chemotherapy or irradiation treatment. Thus, any measure to minimize the risk of infection in this patient population needs to be implemented. We have proposed some preventative measures above but there is a desperate need for further studies to examine further measures.

* These authors answered a different question that was very similar to this one. The consensus voted to remove that question from publication due to its similarity with the current question. Though the question was removed, we want to acknowledge these authors for their work.

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1.3. PREVENTION: RESEARCH CAVEATS

Authors: Rodolfo Capanna, Ivan Bohaček, Lorenzo Andreani

QUESTION 1: What are the significant risk factors for surgical site infection/periprosthetic joint infection (SSI/PJI) of an oncologic endoprosthesis following resection of a malignant bone tumor?

RECOMMENDATION: Patient-related risk factors for SSI/PJI of an oncologic endoprosthesis include increased patients' body mass index, overall presence of comorbidities, coexistence of superficial SSI or skin necrosis and lower preoperative hemoglobin or albumin levels. Disease-related risk factors for SSI/PJI of an oncologic endoprosthesis include lesion localization in proximal tibia, pelvis and lesion extending to pelvis from proximal femur. In addition, procedure related risk factors for SSI/PJI include preoperative hospitalization longer than 48 hours, resection of greater than 37% of the proximal tibia, resection of 3 or 4 heads of the quadriceps muscle in distal femoral lesions compared to 1 or 2 heads, increasing surgical time (longer than 2.5 h), use of cemented oncologic endoprosthesis, need for postoperative admission to the intensive care unit, increased postoperative blood transfusion requirement (2 or more units of allogeneic packed cells), presence of postoperative hematoma and the need for additional surgical procedures after the megaprosthesis implantation.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Periprosthetic joint infection represents one of the most challenging complications following any joint replacement and may result in devastating consequences. According to a recent systematic review, the mean rate of periprosthetic infection of a megaprosthesis (PMI) is 10% after primary procedure and 43% after revision procedures of infected cases [1,2].

Despite the lack of multiple randomized clinical trials, several retrospective studies (Level IV) showed significant risk factors for SSI/PJI of an oncologic endoprosthesis following resection of a malignant bone tumor. In a systematic review of the literature, De Gori et al. examined risk factors for PMI [3]. A total of 8 articles, all retrospective, including 2,136 patients, met the inclusion criteria and were analyzed [4–11]. The overall PMI rate was 14.2%. Patient-related factors associated with a significantly higher risk of PMI included increasing patients' body mass index and overall presence of comorbidities (but not the American Society of Anesthesiolgists (ASA) score or diabetes mellitus specifically) and coexistence of superficial surgical site infection or skin necrosis. Disease-related factors associated with increased risk for PMI included lesion localization in proximal tibia, pelvis and lesion extending to pelvis from proximal femur. In contrast, lesions localized in the distal femur appear to be protective for PMI occurrence. There was no association between primary tumor histological features or metastatic spread and PMI. In addition, there was no significant effect of chemotherapy and radiotherapy for the development of PMI, which is in contrast to several studies [12–15] which report increased incidence of infection rate associated with chemotherapy and radiotherapy. Controversy also still exists regarding whether primary or metastatic lesions have higher risk for PMI [3,12]. In this systematic review, procedure-related factors associated with higher risk of PMI included preoperative hospitalization longer than 48 hours, resection of greater than 37% of the proximal tibia, resection of 3 or 4 heads of the quadriceps muscle in distal femoral lesions compared to 1 or 2 heads, increasing surgical time (longer than 2.5 h), need for postoperative admission to the intensive care unit, increased postoperative blood transfusion requirement (2 or more units of allogenic packed cells), presence of postoperative hematoma and the need for additional surgical procedures after the megaprosthesis

implantation. According to this systematic review, features of perioperative antibiotic prophylaxis do not affect PJI rates, i.e., choice of antibiotic used, dosing, number of antibiotics used postoperatively or length of prophylaxis, which is in contrast to previous systematic review conclusions [1]. In addition, width of resection margins, bone resection length and extracapsular resection of knee tumors were not associated with increased rates of PMI. There was no difference in PMI rates according to prosthesis type or hinge movement, but two studies have shown that cemented megaprostheses have led to a higher PMI rate compared to uncemented ones, thus contradicting information regarding conventional arthroplasties. Routine use of gastrocnemius flap for anterior reconstruction and megaprosthesis coverage following proximal tibia resection has led to a reduced rate of PMI. Data of this systematic review supports the idea that soft tissue condition merely influences the PMI rate [16].

According to a most recent Level III retrospective cohort study on 150 patients, reported by Meijer et al., factors associated with infection after reconstructive shoulder surgery for proximal humerus tumors were lower preoperative hemoglobin or albumin levels and these patients should undergo optimization before surgery [17]. In addition, a lower WBC count and positive resection margins were associated with superficial infection and younger age with deep infection [17]. Furthermore, the location of the endoprosthesis may also influence the infection risk as the lower extremities have been demonstrated to have a greater risk of infection than the upper extremities [15].

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Authors: Roberto Velez, Michelle Ghert, James Yan, Matias Vicente

QUESTION 2: What metrics should be used to determine the optimal timing of reimplantation for patients with a resected oncologic endoprosthesis?

RECOMMENDATION: Prior to reimplantation of an oncologic endoprosthesis after a previous resection, surgeons must ensure that the infection has been eradicated from the surgical bed. This would be determined via a sterile aspirate from the joint cavity following the antibiotic treatment.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Periprosthetic infection following oncologic endoprosthestic limb salvage surgery is a well-recognized and devastating complication [1]. Surgeons who treat oncologic patients with endoprostheses need to have a low tolerance to suspected periprosthetic infection. Oncology patients are at greater risk of infection than general arthroplasty patients, up to 15% of oncological endoprosthetic reconstructions compared to 1-2% within the general population [2,3]. Early diagnosis and treatment are key to outcome. Surgical treatment options include amputation, irrigation and debridement, excision arthroplasty, and one- and two-stage revision, along with targeted antibiotic therapy. Two-stage revision involves initial irrigation, debridement, removal of the endoprosthesis with implantation of a cement spacer and later reimplantation of the device. Despite the established acknowledgement that the two-stage revision is the gold standard for surgical treatment [4], there is a limited amount of information on the clinical parameters that should be used to optimize the reimplantation of an endoprosthesis following initial staged debridement and resection.

A search of the literature found nine retrospective studies, six retrospective cohort studies and three retrospective case studies

TABLE 1. Endoprosthetic infection two-stage revision study data

Study Name	Study Type	Total Number of Patients	Number of Patients Who Developed Infections	Infected Patients Who Underwent Two-stage Revision	Patients With Infections Controlled Successfully (%)
Jeys et al., 2005	Retrospective cohort study	1264	136	58	42 (72%)
Funovics et al., 2011	Retrospective cohort study	170	12	2	2 (100%)
Hardes et al., 2006	Retrospective case study	30	30	15	12 (80%)
Donati et al., 1998	Retrospective cohort study	35	20	19	14 (74%)
Rao et al., 2006	Retrospective cohort study	9	9	9	8 (89%)
Manoso et al., 2006	Retrospective case series	11	11	11	10 (91%)
Grimer et al., 2002	Retrospective case series	34	34	34	25 (74%)

[5–13]. Seven of these studies required clearance of residual infection as determined by a sterile aspirate sample from the periprosthetic space before the revision endoprosthesis could be reinserted [5–11]. These studies showed the success rate of preventing reinfection ranged between 72-100% if reimplantation was conducted using this metric.

The results of four studies following one-stage revision to control infection varied. This approach was performed when the operating surgeons deemed the infection was early in its course or low grade. Funovics et al. reported success rate of 62.5% (5 out of 8 patients) [6]. Jeys et al. found 47% (15 out of 32) of one-stage revisions eradicated the infection [5]. Hardes et al. only found success in 1 out 3 patients (33%) treated with this technique [11]. Holzer et al. reported a success rate comparable to those reported by two-stage revisions at 78% (14 out of 18 patients cleared their infections) [12]. The results of these studies show that the efficacy of one-stage revisions in treating infected oncological endoprotheses is inferior to that of a two-stage approach following negative aspirates. However, the low sample numbers make it difficult to draw a definitive conclusion.

Finally, four of the studies also reported on the importance of adequate soft tissue coverage prior to reimplantation [9–11,13]. This was used as a subjective clinical parameter. Three studies noted that the decision to proceed to the second stage was delayed until adequate soft tissue coverage and wound healing was seen [10,11,13]. Rao et al. noted the influence of different types of soft tissue flaps on infection control in two-stage revisions [9].

Despite the lack of higher quality literature, there has been consistent support by several retrospective studies for using sterile periprosthetic cavity aspirates as a clinical metric to indicate optimal timing for oncological endoprosthesis reimplantation. Other subjective parameters, such as soft tissue coverage and stage of infection, were also recorded. While clearer parameters exist in revision cases for general arthroplasty, more robust evidence, including larger sample sizes and randomized clinical trials, are desired for oncological endoprosthesis. Thus, only a moderate strength recommendation can be provided.

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1.4. PREVENTION: SURGICAL TECHNIQUE

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QUESTION 1: Is there an increased risk for subsequent surgical site infection/periprosthetic joint infection (SSI/PJI) when a drainage tube is used in musculoskeletal tumor surgery?

RECOMMENDATION: Surgical drains should be used selectively in patients undergoing musculoskeletal tumor surgery. If used, they should be continuously monitored and removed immediately once output has decreased adequately per clinical judgment. There is a potential, yet unproven, link between the use of surgical drains and increased risk of SSI/PJI following orthopaedic procedures involving the use of prostheses.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Known risk factors for infection after musculoskeletal tumor surgery include malignancy of the primary tumor, duration of operative time, history of previous surgeries, use of chemotherapy and/or radiotherapy, tumor affectation of the skin and skin necrosis [1]. An additional area of concern in which more information is desired involves the use of surgical drains postoperatively in orthopaedic surgery patients undergoing oncologic procedures. Due to the extensive tissue dissection and exposure needed for musculoskeletal tumor removal, it is not uncommon for drains to be used postoperatively [2–6]. A consensus regarding the risk of SSI/PJI in musculoskeletal tumor surgery due to surgical drain use/duration of the drain remaining in situ has yet to be established.

The relationship between the use of surgical drains and the onset of infection has been examined in previous works. In a review of 723 musculoskeletal tumor surgeries among patients where drains were kept in 2-3 days (non-pelvic tumors) and 5 days (pelvic tumors), Rossi et al. found an overall infection rate was 8.7% [5]. Literature has a tendency to signal drainage tubes increase infection risks in musculoskeletal tumor surgeries. This may be due to the fact that they connect the endoprosthesis or the site affected by the tumor with the outside flora, thus making colonization by microorganisms, such as *Staphylococcus aureus*, more likely. Rates of SSI, with skin flora bacteria, such as *S. aureus*, have been increasing over the last decade. The exact reason for this increase is unknown but could relate to the use of surgical drainage in patients undergoing musculoskeletal tumor surgery [6].

To date, there is no consensus on how long surgical drains should remain in place after surgery and whether or not they contribute to the risk of orthopaedic oncology patients developing SSI/PJI. Per the World Health Organization (WHO), low-quality evidence shows the early removal of wound drains has neither benefit nor harm in reducing the SSI rate when compared to its late removal among any patient undergoing a surgical procedure [7]. Lerman et al. conducted a retrospective review of 165 patients with musculoskeletal tumor surgeries [3]. In their cohort, 10.3% of all patients had 2 surgical drains remain intact 24 hours postoperatively. However, surgical drain usage was not accounted for in the study's univariate analysis. In Shehadeh et al.'s retrospective review of 232 patients, overall infection rates in the group were similar at 11.36% [4]. In their protocol, drain tubes were removed when their debit was less than 30cc since the last shift. As with Lerman et al.'s study, commentary cannot be made regarding the influence drain usage had on the rate presented, because it was not accounted for in the study's statistical analysis.

Further insight can be obtained by a meta-review done by the WHO. Thirty-four systematic reviews investigating the effect of drains compared to no wound drainage in terms of the related infection risk in patients undergoing various surgical procedures were reviewed [7]. Review of the meta-analyses showed a tendency towards a beneficial effect of not using a wound drain with regard to a reduced risk of wound infections with no statistical significance. One of the few proven benefits of drains is a reduced need for a change of the dressing and increased comfort (observed among patients receiving total hip arthroplasty) [8,9]. Taking these factors into consideration and current status of the literature, decision making is to be made at the discretion of the clinician at this time. Further investigation into surgical drain use and its influence on SSI/PJI in musculoskeletal tumor surgery is warranted.

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QUESTION 2: When should a surgical drain be removed to minimize the risk of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI) in patients who have received endoprosthetic reconstruction (EPR) following resection of a musculoskeletal tumor?

RECOMMENDATION: Based on the available literature, we recommend drains be removed within 24 hours of surgery.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Drains are plastic tubes that are used to prevent the formation of surgical site serous pockets (seromas) and blood pockets (hematomas), both of which may act as a space for potential surgical site infection in addition to causing pain [1]. In orthopaedics, drains are commonly used to reduce collection of fluid around the joint and potentially reduce subsequent SSIs despite little evidence showing their benefit [2,3]. The utilization of closed suction drainage systems in primary arthroplasty has been debated for many years. Anecdotally, the benefits of a drain are thought to be prevention of hematoma formation and therefore improved wound healing and decreased infection rates [2]. The main disadvantage is the creation of a communication between the deep tissues and the surrounding environment, providing a conduit for bacterial contamination [2]. In fact, drains are known to be risk factor for SSIs [4]. Patel et al. have reported a relative risk increase in SSIs of 42% with each additional day of wound drainage [5]. Despite the scarcity of evidence supporting their benefit and known risks, orthopaedic surgeons continue to utilize drains in their procedures [6].

PJI rates after elective total joint replacement are reported between 1-2% [7,8]. However, the risk of PJI following EPR is even higher with rates ranging between 10-25% [9,10]. Because drains are a known risk factor for SSIs, their use in orthopaedic oncologic procedures is of particular concern. Oncology patients are at increased risk because many of them are immunocompromised. Secondly, this patient population often develops a large dead space after tumor resection necessitating placement of a surgical drain to prevent hematoma formation in the postoperative period.

A large meta-analysis of all randomized controlled trials of drain use in orthopaedic surgery was published by Parker et al. in 2004. They found no significant difference between wounds treated with and without drains with respect to the development of wound infection, wound hematoma or reoperations for wound complications [11]. However, the drained wounds did have a significantly greater need for blood transfusion [11]. These overall findings have been shown in numerous other studies of patients undergoing arthroplasty, general surgical and orthopaedic trauma procedures [12–14].

In 2007, a Cochrane Systematic Review was conducted to assess the utilization of drains in orthopaedic surgery. Thirty-six studies involving 5,464 patients with 5,697 surgical wounds were included [2]. Many orthopaedic procedures were utilized, although there was no specific mention of oncologic patients in the review. Pooling of results showed no statistically significant difference in the incidence of wound infection, hematoma, dehiscence or reoperation between those who had a drain and those who did not [2]. The incidence of SSI was 1.9% in patients who received a closed suction drain and 2.4% in those who did not [2]. Blood transfusions were required more frequently in those who received drains [2]. Previous literature has found an association between blood transfusion and infection in both the arthroplasty and orthopaedic oncology literature [15,16]. Despite the described findings of previous literature and the increased blood transfusions in the drain group, an independent relationship between drain placement and infection was not found in the Cochrane review [2].

In terms of the timing of drain removal, the literature remains inconclusive. In their prospective study of 214 uninfected orthopaedic operations, Sankar et al. found no significant correlation between wound infection and duration of drain retention [17]. Another prospective study examined total hip and knee arthroplasty patients who all received suction drains. Upon drain removal, the patients' drain-sites were swabbed and the drain tips were sent for culture [18]. This study demonstrated that the likelihood of bacterial colonization increased while wound drainage decreased over time; however, this does not necessarily translate to clinical development of SSI and their recommendation for removal at 24 hours must be cautiously considered [18].

Willett et al. attempted to further examine the timing of drain removal by removing drains at 24, 48 or 72 hours and culturing the aspirates taken from the drain tip; they found increasing rates of positive cultures in the groups where the drain was removed later. However, this difference was not statistically significant [19]. The authors of this study conclude that their data affirm the risk of retrograde influx of organisms along the drain track if the drain remains in place longer than 24 hours [19]. However, because their results were not statistically significant, they were incorrectly drawing this conclusion.

From the arthroplasty and surgical literature, there is no evidence of benefit to extending antibiotic duration until drains are removed; however, this has not specifically been evaluated in a musculoskeletal oncology patient population [20,21]. Due to the scarcity of quality literature in this area and the lack of evidence suggesting a relationship between utilization of drains and SSI, an evidence-based recommendation regarding the use of drains and the timing of their removal cannot be made for orthopaedic oncology patients.

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QUESTION 3: Does the type of fixation (cemented vs. uncemented) of an oncologic endoprosthesis influence the incidence of subsequent surgical site infection/periprosthetic joint infection (SSI/PJI)?

RECOMMENDATION: There is conflicting evidence surrounding this topic. Multiple studies have demonstrated superiority with cemented fixation of an oncologic endoprosthesis while others have suggested superiority with uncemented fixation. Therefore, the choice of the method of fixation should be made on the basis of all clinical indications, other than the influence of fixation on subsequent SSI/PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Limb salvage surgery has become the treatment of choice for musculoskeletal cancers due to advances within the field of orthopaedic oncology. The use of an oncologic endoprosthesis has become the procedure of choice in limb salvage surgery. Though there are many benefits in utilizing an endoprosthesis, the development of subsequent infection is one of the most common and feared complications.

Multiple studies have been conducted to examine the risk of postoperative infection associated with the type of fixation (cemented vs. uncemented). Moreover, the approval and universal use of antibiotic-impregnated cement has altered the landscape as it relates to the risk and type of infection.

A systemic review of 40 studies examining distal femoral replacement (DFR) cases and proximal tibial replacement (PTR) cases showed mixed results. One hundred and nine (5.8%) of 1,894 cemented DFR cases became infected while 65 (9.0%) of 721 uncemented DFR cases became infected. This difference was found to be statistically significant [1]. For cemented DFR replacements, linear regression analysis showed that the risk of infection increased over time ($p < 0.001$), but the risk for infection in uncemented DFR implants did not increase over time. The same systemic review showed that 109 (15.2%) of 716 cemented PTR cases became infected while 56 (14.1%) of 396 uncemented PTR cases became infected; this difference was not found to be statistically significant. The incidence of infection in PTR cases did not increase over time, regardless of the fixation method [1].

Pala et al. [2] reported that 20 (9.1%) of 220 endoprostheses originally implanted in patients with either a lower extremity primary bone tumor or metastatic disease became infected. Of these 20 cases, 12 (10.3%) were cemented and eight (7.7%) were uncemented. In addition, survival of cemented endoprostheses to infection was 68% at 60 months, while survival of the uncemented endoprostheses was 82% at 60 months [2]. Finally, in both univariate and multivariate analyses, the only variable that was found to be a predictor of survival was uncemented fixation [2].

The infection rates of endoprostheses vary widely in the literature. Studies investigating the infection rate after cemented fixation of an endoprosthetic device yielded an infection rate ranging from 5.2% to 21.9% [3–7]; studies investigating the infection rate after uncemented fixation yielded rates ranging from 9.7% to 12% [8–10]. A condition of equipoise exists resulting from the conflicting data supporting cemented or uncemented fixation and the incidence of subsequent SSI/PJI.

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QUESTION 4: Does the use of incise draping with antibacterial agents (iodine) influence the risk for subsequent surgical site infection/periprosthetic joint infection (SSI/PJI) in patients undergoing musculoskeletal tumor surgeries?

RECOMMENDATION: There is some evidence claiming that antimicrobial-impregnated incise drapes result in a reduction in bacterial contamination at the surgical site. However, there is little evidence to demonstrate that it results in a subsequent reduction in the incidence of SSI and/or PJI.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Surgical incise drapes are often used by surgeons to reduce bacterial recolonization of the surgical site with host flora that may potentially predispose the patient to subsequent infection. Furthermore, it is important to differentiate antimicrobial-impregnated drapes from non-impregnated drapes as the addition of an antimicrobial agent, such as iodophor, may have a different effect on the rate of recolonization. The rationale behind the antimicrobial drape is that the incise drape can act as a physical barrier to block bacterial proliferation on the skin and potential entry into the surgical wound.

Multiple studies have demonstrated that incise drapes can result in a reduction in bacterial recolonization. In a prospective randomized controlled trial of 101 hips undergoing hip preservation surgery, Rezapoor et al. found that iodine-impregnated drapes resulted in a significant reduction (12.0% vs. 27.4%) in bacterial colonization compared to those without drapes [1]. Furthermore, Milandt et al. reported that the use of iodine-containing incision drapes did not increase bacterial recolonization in simulated total knee arthroplasty [2]. Dewan et al. reported that the use of an iodophor-impregnated plastic incise drape in abdominal surgery reduced the contamination of the wound [3]. Casey et al. evaluated the antimicrobial efficacy of an iodine-impregnated incise drape against methicillin-resistant *S. aureus* (MRSA) in a skin model and concluded that it had detectable antimicrobial activity [4].

While there is evidence to suggest that impregnated incise drapes result in a reduction of bacterial colonization, there is conflicting evidence demonstrating that impregnated incise drapes result in a significant decrease in the infection rate. Ritter et al. demonstrated a considerably low rate of SSI incidence (0.46%) in total arthroplasties performed with an antimicrobial incise drape [5]. In addition, Yoshimura et al. found that the lack of an iodophor-impregnated drape was a significant risk factor for wound infection after liver resection [6]. In contrast, a randomized study by Dewan et al. suggested that iodine-impregnated drapes did not result in a significant reduction in SSI rate in abdominal and cardiac surgery [3]. Furthermore, a randomized study by Segal and Anderson showed only a tendential reduction in the rate of SSIs by iodophor-impregnated adhesive drapes in high risk cardiac surgery [7]. Additionally, no SSIs were observed in a retrospective review of 581 patients undergoing anterior cervical fusions without iodophor-impregnated incision drapes. It was concluded that the use of iodophor-impregnated incision drapes during anterior cervical fusion was not needed [8].

In a Cochrane review of 3,082 patients, Webster et al. found that a higher proportion of patients developed surgical site infection with plastic drapes than patients in whom no drapes were used ($p = 0.03$) [9]. However, no difference was found when iodophor-impregnated drapes were used (rate ratio (RR) 1.03, 95% confidence interval (CI) 0.06 to 1.66, $p = 0.89$), which further highlights the importance of discriminating between antimicrobial and regular plastic incise drapes. In the World Health Organization guideline [10], four of the above-mentioned studies (one randomized-controlled trial (RCT) [7], one quasi-RCT [11] and two observational studies [6,12]) were identified that assessed the effect of using single-use adhesive incise drapes to reduce SSI. They commented that the two RCTs showed the use of antimicrobial-impregnated incise drapes may have some adverse effect, but the effect estimate was not statistically different from the control group. Furthermore, they noted that the observational studies reported that there may be a benefit in using antimicrobial-impregnated incise drapes, but the effect was not statistically different from the control group. They concluded that the quality of evidence for these comparisons was very low for both the randomized control trials and the observational studies due to the risk of bias and imprecision or inconsistency.

There is an extensive number of publications demonstrating that the use of antimicrobial-impregnated incise draping leads to a lower incidence of surgical site contamination. Studies demonstrating the beneficial effect of incise draping in reduction of surgical site infection, especially after tumor surgery, are lacking.

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QUESTION 5: Does the use of soft tissue attachment meshes increase the risk for subsequent periprosthetic joint infection (PJI) in patients undergoing oncologic endoprosthetic reconstruction?

RECOMMENDATION: The current literature indicates that there is no increased risk of PJI in this patient population with the use of soft tissue attachment meshes. However, there are few studies directly comparing the use of mesh vs. not using mesh in comparable tumors/surgical locations, so further comprehensive study on the topic is necessary to say with reasonable certainty that there is no connection.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The reported infection incidence after tumor resection and replacement with an endoprosthesis varies widely in the literature, ranging from 7.8% to 25% [1–3]. Tumor type and surgical site have a significant influence on the infection incidence [3,4]. Despite the variation reported in the literature, the infection burden for these procedures is much greater than that of primary joint replacement surgery for which the infection rate of hips and knees is estimated at 1% [5].

Infection in endoprosthetic reconstruction cases has been attributed to multiple sources, one of which is the use of surgical mesh. Surgical mesh has been suggested to act as a vehicle for infection. This risk is increased when the mesh is used alongside a large implant or neoadjuvant chemotherapy. Henderson et al. investigated complication incidence in a series of 534 endoprosthetic failures and found that infection was the most common mode of failure [4]. Cho et al. examined risk factors related to infection in a cohort of 62 patients who underwent proximal tibial endoprosthetic reconstruction. Prostheses were removed due to infection in 25.8% of the patients; however, application of synthetic mesh to stabilize the patella was not found to be a significant risk factor, nor was chemotherapy [1]. A 2017 study investigated patient outcomes using BARD® mesh for endoprosthetic reconstruction and reported that only one case of deep infection and two cases of superficial infection developed out of 51 patients [6]. A systematic review of reconstruction techniques after resection of proximal humeral tumors found that megaprosthesis with mesh had an infection rate of 4%, which was between the rates of hemiarthroplasty (0%) and reverse shoulder arthroplasty (9%) [7].

Polyethylenterephtalate mesh, known as a Trevira® tube, is a mesh option used for endoprosthetic reconstruction. A 2001 study of 69 megaprostheses implants with Trevira tube for soft tissue reconstruction reported that there was no significant increase in the rate of infection compared to implantation without a Trevira tube [8]. Similarly, Maccauro et al. examined a cohort of 36 patients with solitary bone metastases who underwent resection and endoprosthetic reconstruction, of which 20 of the patients received a Trevira tube. They also detected no significant difference in infection rate between patients who did and did not receive a Trevira tube [9]. Additionally, Schmolders et al. determined that replacement of the proximal humerus using a Trevira tube in combination with a modular endoprosthesis is a safe and viable treatment option for both bone tumors and metastases. They observed no statistically significant increased risk of infection by using a Trevira tube, even among immunosuppressed patients [10].

Surgical meshes for reconstruction of abdominal wall hernias and groin region hernias have been successfully used since the 1940s [11]. While abdominal hernia repairs do not incur the additional

infection risks of endoprosthesis implantation and immunosuppressive effects of neoadjuvant therapy, patient outcomes using synthetic mesh for abdominal hernia repair have been well studied and provide some insight regarding infection rates associated with the use of mesh. A recent meta-analysis of 10 randomized controlled trials comparing abdominal hernia surgery outcomes using mesh vs. surgical suture detected no significant difference in infection rates between the 2 groups. However, the mesh group did demonstrate significantly lower incidence of recurrent hernia than the surgical suture group, leading the authors to conclude synthetic mesh was a highly efficacious repair technique [12].

In summary, the published literature suggested little or no association between the use of mesh for soft tissue attachment with endoprosthetic reimplantation and development of subsequent PJI. Further study is needed before it can be conclusively determined that the use of soft tissue attachment meshes does not increase the risk for subsequent infection in patients undergoing oncologic endoprosthetic reconstruction. Future investigation should utilize larger cohorts and control for tumor type and location so that the use of mesh can be better isolated as the variable of interest.

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QUESTION 6: Should endosprosthesis and/or allograft bone be soaked in antibiotic solution or antiseptic solutions prior to implantation in patients?

RESPONSE: Unknown. There is no evidence to suggest that the use of a pre-implantation antibiotic or antiseptic soak of an endoprosthesis or massive allograft would reduce the rate of surgical site infection/periprosthetic joint infection (SSI/PJI).

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

In the oncologic literature, infection rates following metallic endoprostheses and bulk allograft surgery are high. In a systematic review, Henderson et al. found the rate of infection-related failure of endoprostheses to be 7.4%, when all anatomic locations were taken into account. Proximal tibia replacements and total femur replacements were noted to be at particular risk for infection, requiring revision surgery in 19.7% and 17.5% of cases, respectively [1]. In a systematic review of pediatric oncology patients, Groundland et al. found an infection rate of 12.9% and 17.1% when bulk osteoarticular allografts were used to reconstruct the distal femur and proximal tibia, respectively [2].

While not fully understood or rigorously investigated, the causes of these high rates of infection are likely multi-factorial, including extensive surgical dissections and resections, substantial blood loss, implantation of large constructs with foreign material and, in the case of oncology patients, a potentially immunosuppressed host.

Any measure that leads to decreased infection rates of metallic endoprosthesis and massive allograft reconstruction would be desirable. Given the prevalence of the problem and the severity of the consequences of deep infection, even weak evidence supporting a decrease in infection rates would be worth considering. While a few interventions have been noted to be beneficial, as reported in retrospective case series, no rigorous, prospective studies have been completed in this population [3–8]. Regarding the question above, there is no evidence to support or reject the use of a pre-implantation antiseptic soak of the endoprosthesis (or allograft). Local application of an antibiotic solution (e.g., gentamicin) around prosthesis before closing the incision in conjunction with a parenteral agent as antibiotic prophylaxis is routine practice in some institutions [9]. However, antibiotic solutions have been found to offer no advantage over saline in the removal of bacteria from bone, titanium or stainless steel. In addition, there

are no efficacy data to support the use of antibiotic soaks in procedures with sterile prosthesis insertion [10,11]. There are no high quality trials testing the effectiveness of antiseptic soaking of prosthesis before implantation [12]. Moreover, antiseptics could exert changes in materials used for total arthroplasty (e.g., titanium alloy or hydroxyapatite), cause chondrolysis or pose cytotoxicity to human fibroblasts and osteoblasts [13,14].

Conceptually, a pre-implantation soak would decrease the bacterial load on the implant immediately prior to implantation, thereby reducing the risk of an infection caused by direct seeding of the wound bed by the implant itself. In an in vitro study bone fragments soaked with a solution of gentamicin or vancomycin for 30 minutes were loaded with an antibiotic concentration, 5-fold the minimum inhibitory concentration (MIC) values would be needed to provoke bacterial regression [15]. It has been also shown that in vitro decontamination of bone allografts contaminated with coagulase-negative Staphylococci is feasible after soaking bone with gentamicin or rifampicin for 60 minutes [16]. However, clinical studies are lacking, and there are no randomized controlled trials or systematic reviews that have evaluated soaking endoprosthesis or allograft bone in antibiotic or antiseptic solutions before implantation for the prevention of surgical site infections [17]. Two facts belie this practice. First, there is no published evidence that sterilized implants (endoprosthesis or allograft) routinely become colonized or contaminated from their unpackaging to implantation. Second, most infections in endoprosthesis and massive allograft surgery do not manifest in the perioperative period; rather, the average time to failure due to infection occurs years after the index surgery. In their report of 2,174 endoprosthesis surgeries, Henderson et al. reported an overall time revision surgery due to infection of 47 months, with a non-normally distributed standard deviation of 69 months [1]. The anatomic location with the fastest time to infection-driven revision was the elbow, occurring at a mean of 16 months, while the proximal humerus had an infection time of 80 months. A pre-implant soak would have no theoretical impact on these late infections.

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QUESTION 7: Should a coated prosthesis (silver/iodine) be used for reconstruction of patients undergoing primary bone tumor resection?

RECOMMENDATION: Yes, silver coating and iodine coating of prosthesis show good results in prevention of infection after reconstruction following primary tumor resection.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Megaprosthesis has been used to reconstruct limbs and large skeletal defects after resection of bone tumors for many decades. A significant problem is the higher rate of infection as compared to an infection rate of < 1% after a standard primary arthroplasty procedure. Many factors have been cited in literature which include length of surgery, OR environment, blood transfusions, soft tissue available for coverage and segment involved, e.g., tibia vs. femur. The average infection rate reported in literature is 10% (range 0–25%).

TABLE 1. Major findings and conclusions in the literature on silver-coated megaendoprostheses*

Author, Reference	Journal, Year	Study Design	Patients (*n*)	Results	Conclusion
Gosheger et al. [16] Silver-coated megaendoprostheses in a rabbit model: analysis of infection rate and toxicological side effects	Biomaterials 2004	Animal trial	30 (silver n = 15, titanium n = 15)	The silver group showed significantly ($p < 0.05$) lower infection rates (7% vs. 47%) in comparison with the titanium group after artificial contamination with S. aureaus	The new silver-coated MUTARS megaprosthesis resulted in reduced infection rates in an animal trial
Hardes et al. [27] Lack of toxicological side effects in silver-coated megaprostheses in humans	Biomaterials 2007	Prospective	20	No sign of toxic side effect after implantation of silver-coated megaprostheses. The silver levels in blood were considered non-toxic. No changes in liver or kidney function	Silver coatings on megaprostheses show no local or systemic side effects
Hardes et al. [9] Reduction of periprosthetic infection with silver-coated megaprostheses in patients with bone sarcoma	Journal of Surgical Oncology 2010	Prospective (silver group); retrospective (titanium group)	125 (silver n = 51, titanium n = 74)	The infection rate was substantially, but not significantly, reduced from 17.6% in the titanium group to 5.9% in the silver group. Included were patients with a proximal femur or proximal tibia replacement	Using silver-coated prostheses reduced the infection rate over the medium term
Glehr et al. [28] Argyria following the use of silver-coated megaprostheses: no association between development of local argyria and elevated silver levels	Bone and Joint Journal 2013	Retrospective	32	Asymptomatic local argyria in 23% of patients with silver-coated megaprostheses. No systemtic toxicity due to silver	However, the majority of the patients received silver-coated prostheses in revision, so that due to a negative pH value, increased release of Ag+ ions may be suspected
Wafa et al. [31] Retrospective evaluation of the incidence of early periprosthetic infection with silver-treated endoprostheses in high-risk patients: case-control study	Bone and Joint Journal 2015	Retrospective	170 (silver n = 85, titanium n = 85)	This retrospective study showed a postoperative infection rate of 11.8% in the group with silver-coated prostheses vs. 22.4% in the group with uncoated prostheses ($p = 0.033$)	Silver-coated implants showed a reduced reinfection rate after PJI in two-stage revisions (success rates of 85% in sliver group compared to 57.1% in uncoated group, $p = 0.05$)
Politano et al. [20] Use of silver prevention and treatment of infections: silver review	Surgical Infections 2013	Review	--	Benefits of silver-coated orthopaedic prostheses are still unproved	
Wilding et al. [32] Can a silver-coated arthrodesis implant provide a viable alternative to above-knee amputation in the unsalvageable, infected total knee arthroplasty?	Journal of Arthroplasty 2016	Retrospective	8	With a mean follow-up period of 16 months (5-35 months), only one patient had recurrent infection, but prosthesis-preserving treatment was possible	The silver-coated arthrodesis is a good alternative to amputation, particularly in infected knee prostheses

*Adapted from Schmidt-Braekling T, Streitbuerger A, Gosheger G, Boettner F, Nottrott M, Ahrens H, et al. Silver-coated megaprotheses: review of the literature. Eur J Orthop Surg Traumatol. 2017;27(4):483–489.

Silver coating of prosthesis is one of the methods studied so far. A number of retrospective studies have reported a decrease in the infection rate following use of silver-coated endoprosthesis. However, evidence from prospective and randomized trials is lacking [1]. See Table 1.

The Kanazawa group developed an iodine coating and published their results for the first time in 2012. In their study, 222 patients received iodine-coated implants of which 64 had active infection [2]. Their results suggest an even greater efficacy in prevention of infection as compared to silver coating interval and even eradication of infection in cases with active infection. Subsequent reporting by the same group in 2014 has also shown greater efficacy of iodine-treated implants in patients with trauma, bone loss due to infections and tumor resection as well as revision setting with previously infected implants [3].

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QUESTION 8: What is the most optimal local antimicrobial delivery strategy during limb salvage: antibiotic cement, silver-coated implant, iodine-coated implant, topical vancomycin powder, injection of antibiotics via drain tubing or other?

RECOMMENDATION: Unknown. No direct comparison has been made of different antimicrobial delivery strategies in oncological patients undergoing limb salvage procedures.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Surgical excision of primary malignant tumors and metastases of the bone frequently leads to large skeletal defects. While once amputation was typically the only solution, the introduction of megaprostheses and later modular megaprostheses has led to limb salvage becoming the standard of care [1]. Despite falling rates of mechanical failure, the risk of periprosthetic infection remains high in comparison with conventional arthroplasty [2]. Treatment of periprosthetic infections often requires surgical intervention and prolonged antibiotic therapy [3]. Ongoing efforts directed at finding an effective means of infection prophylaxis have been examined exclusively in small observational studies without direct comparison between methods, thus limiting their conclusions.

Published studies appear to support the use of silver-coated implants. Data exist for limb salvage in sites including the hip, proximal and distal femur, pelvis, proximal and distal tibia, humerus and radius [4–10]. Six cohort studies, all but one retrospective, compared oncological patients who received silver-coated implants with non-coated (mostly titanium) implants [4–8,10]. The results across the studies were uniform with fewer patients who received silver-coated implants developing periprosthetic infections than the patients who received non-coated prostheses.

Weak evidence from a single retrospective cohort study indicates that alloy-type megaprosthesis may influence the risk of subsequent infection [11]. Significantly more patients who received a cobalt-chrome prosthesis developed infection than patients who received titanium prostheses.

Very weak evidence exists suggesting that iodine-coated megaprostheses may reduce risk of periprosthetic infection [12]. Similarly, there are limited data supporting the use of iodine-coated hardware in patients undergoing reconstruction [13].

Despite the body of evidence on antibiotic-impregnated cement in arthroplasty, only one case series examined its effects specifically in orthopaedic oncology patients who underwent total knee prostheses [14].

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Treatment

2.1. TREATMENT: IRRIGATION AND DEBRIDEMENT

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QUESTION 1: How many irrigation and debridements (I&Ds) of an infected oncologic endoprosthesis are reasonable before consideration should be given to resection arthroplasty?

RECOMMENDATION: Decision to repeat irrigation and debridement and retention of an infected endoprosthesis (DAIR) should be made based on comorbidities of the host, virulence of the organism, complexity of the reconstruction and status of the soft tissues. We believe DAIR performed more than two or three times is unlikely to be successful.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The utilization of musculoskeletal tumor surgery has increased through the years thanks to the increase in therapeutic alternatives. One of these alternatives is resection of the tumor and implantation of a tumor endoprosthesis. These surgeries are complex, long and aggressive for the surrounding tissues. There are many possible complications following these procedures, of which periprosthetic joint infection is one of the most feared.

Infection rates in primary musculoskeletal surgeries have been reported from over 5% to over 15% [1,2]. Several risk factors have been identified, including malignancy of the primary tumor, surgical time, previous surgery, the use of chemotherapy and/or radiotherapy, tumor affectation of the skin and skin necrosis [3]. Identification of these factors is crucial because the onset of infection increases the rate of morbidity, mortality, the number of subsequent procedures and amputation [4].

The optimal treatment for oncologic endoprosthesis infection is currently a matter of debate. Several authors have investigated the role of DAIR, including the number of attempts that should be made before undergoing more aggressive surgery.

Dhanoa et al. [5] reviewed 105 patients with oncologic endoprosthesis infections. In their experience, I&D could be performed when the case met the following criteria: acute onset infection (14–28 days), clear-cut diagnosis based on histopathology and microbiology, stable implant and susceptibility of the microorganism to an effective orally-available antimicrobial agent. With this method they reported a 42.8% rate of infection eradication. In those patients in which debridement failed, a two-stage revision surgery would be performed without trying a second debridement. A similar therapeutic strategy was demonstrated by Kapoor et al. [6]. Patients would undergo as much as one surgical debridement before switching to two-stage revision if the debridement had failed. Both authors agree that late prosthetic infections are associated with poor results when treated by lavage, debridement or prolonged antibiotics administration. Therefore, removal of the infected prosthesis either as one- or two-stage procedure, resection arthroplasty or an amputation becomes necessary. Funovics et al. [2] reported a 50% eradication rate after surgical debridement. In their experience, when debridement alone failed, one-stage revision surgery was performed.

Not all authors view debridement as an inferior method in treating endoprosthetic infection, however. Allison et al. [7] treated 329 musculoskeletal tumors and reported a 13.9% overall infection. Although they did not clarify how patients were selected for each treatment method, they reported a 70% healing rate after single-stage irrigation and debridement with exchange of the modular component and varying degrees of suppressive antibiotics. That healing rate was superior to the one they achieved after revision, antibiotic spacer placement and subsequent reimplantation (62%). On the other hand, Jeys et al. [8] claim that I&D alone has a poor outcome in endoprosthetic infection. After treating 136 patients, they reported only a 6% eradication rate after debridement only. They also state that healing after resection arthroplasty was achieved in 50% of cases, but they do not specify the reason why patients were treated one way or another.

Not all authors believe that surgical debridement should be a step in management of oncologic endoprosthesis infection. Holtzer et al. [9] treated 18 patients with endoprosthetic infection. They considered debridement a poor option and thus performed one-stage revision surgeries in all cases. Infection was eliminated in 14/18 patients (77.78%). In a similar manner, Hardes et al. [10] treated 30 patients and developed a therapeutic algorithm for oncologic endoprosthesis infection that did not include I&D. They believed that one-stage revision surgery should be performed whenever possible. If one-stage revision is not possible, then two-stage revision should be performed. If two-stage revision is not possible, then arthrodesis should be performed. Finally, if arthrodesis is not possible, then amputation should be performed. Out of 30 patients, 19 (63.33%) were cured with a one- or two-stage revision. Of the remaining 11, amputation was performed in 6/30 (20%).

In conclusion, it is unclear if I&D serves as a good alternative for the treatment of an infected endoprosthesis. In addition, the number of attempts that should be made towards I&D before revision surgery or amputation is uncertain. It seems that for acute infections with an antibiotic–sensitive microorganism, debridement

may be a good first step in the treatment algorithm, but failure rates are high, and no more than two surgical debridements should be attempted before considering a revision surgery in order to achieve infection eradication.

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QUESTION 2: How should acute reinfection of an oncologic endoprosthesis be treated?

RECOMMENDATION: Acute reinfections in patients with oncologic endoprostheses demand treatment by surgical methods because the long-term administration of antibiotics alone is not sufficient. The most appropriate treatment modality for acute re-infection is debridement, antibiotics and implant retention (DAIR) with exchange of components.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Oncology patients represent a high-risk subset of the population. The implantation of endoprostheses in this cohort of patients leads to an increased risk of infection due to their immunocompromised state, previous radiotherapy, poor soft tissues, poor nutritional status or significant comorbidities [1].

Many options have been proposed to prevent infections of an endoprostheis. However, there are no current appropriate guidelines or recommendations to guide optimal management of an acute endoprosthetic reinfection. There is a paucity of literature regarding the results of these different procedures, though it has been shown that irrigation, debridement and prolonged antibiotic administration have the poorest results in treating late prosthetic infections [2]. Therefore, removal of the infected prosthesis either as one- or two-stage procedure or an amputation may be necessary [2].

Allison et al. reviewed 329 patients who had undergone arthroplasty surgery for definitive oncological treatment [3]. Of those that became infected and were treated with irrigation and debridement without component exchange, there was a 42% success rate at eradicating infection. With single stage exchange, this increased to 70%. Two-stage revision led to a 62% success rate. Conversely, previous literature has associated two-stage revisions as having a higher success rate when compared with one-stage [4–6]. As one would expect, amputation has been shown to carry the highest rate of infection eradication. The risk of amputation due to an infected endoprosthesis has been reported to be between 23.5% and 87% [4,7,8].

Periprosthetic infection can lead to a poor functional outcome as well as an increased morbidity and mortality. Management of infections after reconstructive surgery for bone tumors is a challenge, requiring careful planning, consideration of the patient's prognosis and a potentially aggressive surgical approach.

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QUESTION 3: Is irrigation and debridement and exchange of modular parts a viable option for treatment of acute periprosthetic joint infection (PJI) involving oncologic endoprosthesis? If so, what are the indications?

RECOMMENDATION: Yes. Irrigation and debridement with retention of prosthesis (DAIR) is a viable option for management of patients with infected endoprosthesis. The procedure may be offered to patients with superficial early infection (< 3 months), short duration of symptoms (< 3 weeks), well-fixed implants and well-characterized organism demonstrating a highly susceptible pathogen.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Surgical reconstruction using an endoprosthesis after tumor resection is frequently associated with deep surgical site infection that leads to PJI. The prevalence of PJI associated with oncologic endoprosthesis is 7-28% compared to only 1-2% in primary joint replacements. Cancer patients are at a higher risk for developing PJI after receiving an endoprosthesis due to numerous risk factors, which lead to local and systemic immunodeficiency. These risk factors include chemotherapy, radiotherapy, prolonged surgical time, increased bleeding, larger implant surface area and compromised soft tissue envelope.

In case of an infected oncologic endoprosthesis, debridement, antibiotics and implant retention (DAIR) can be performed, especially in early acute infections (< 3 months). If DAIR fails to eradicate the infection, a two-stage revision is necessary. In the literature, two-stage revision is generally reported as a good surgical approach for infection control with a reported success rate of 63-100% [1–6]. Eradication of infection is generally worse after a single-stage revision and, of course, better after an amputation [4,7–9].

In order to optimize the treatment of patients with an infected oncologic endoprosthesis we performed a literature search to assess factors associated with successful eradication of the infection after DAIR. Although various studies assessed infection of oncologic endoprostheses, only few specifically evaluated the efficacy of DAIR [2,3]. We assessed the literature for indications as well as factors that influenced the treatment outcomes of DAIR. Due to the lack

TABLE 1. PubMed relevant search terms

Database	Search Terms	Total
PubMed English Until 01 Feb 2018	PICO 1a: (((((infection) AND ((prosthetic joint OR endoprosthes* OR arthroplast* OR megaprosthes* OR tumourprosthes* OR tumorprosthes*))) AND ((oncolog* OR tumour OR tumor)))) AND ((two stage OR revision))) AND ((antibiotic* OR antimicrobial* OR holiday period))	39
	PICO 1b: ((((((prosthetic joint OR endoprosthes* OR arthroplast* OR megaprosthes* OR tumourprosthes* OR tumorprosthes*))) AND ((oncolog* OR tumour OR tumor))) AND ((two stage OR revision)))) AND ((chemo OR chemotherapy))	67
	PICO 1c: ((((((prosthetic joint OR endoprosthes* OR arthroplast* OR megaprosthes* OR tumourprosthes* OR tumorprosthes*))) AND ((oncolog* OR tumour OR tumor))) AND ((two stage OR revision)))) AND radiotherapy	23
	PICO 1d: ((((((prosthetic joint OR endoprosthes* OR arthroplast* OR megaprosthes* OR tumourprosthes* OR tumorprosthes*))) AND ((oncolog* OR tumour OR tumor))) AND ((two stage OR revision)))) AND ((micro-organism OR bacter* OR culture))	44
	PICO 1e: ((((((prosthetic joint OR endoprosthes* OR arthroplast* OR megaprosthes* OR tumourprosthes* OR tumorprosthes*))) AND ((oncolog* OR tumour OR tumor))) AND ((two stage OR revision)))) AND spacer	19
	PICO 1f: (((((((prosthetic joint OR endoprosthes* OR arthroplast* OR megaprosthes* OR tumourprosthes* OR tumorprosthes*))) AND ((oncolog* OR tumour OR tumor))) AND ((two stage OR revision)))) AND infection)) AND silver	10
	PICO 2: ((((prosthetic joint OR endoprosthes* OR arthroplast* OR megaprosthes* OR tumourprosthes* OR tumorprosthes*))) AND ((oncolog* OR tumour OR tumor))) AND ((DAIR OR debridement OR irrigation OR washout))	74

TABLE 2. Evidence table

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Bus 2017 [17]	Retrospective cohort 2008–2014	N = 47 LUMIC reconstruction for pelvic tumor	* 69% DAIR * 31% implant removal	3.9 years	* 28% had infection. * 69% were successfully treated with DAIR (2). * 31% needed implant removal. Two had amputation, one rotationplasty and one LUMIC prosthesis. * More blood loss was associated with a higher risk of infection; other factors were not associated.
Chambers 1962 [18]	Narrative review	X	X	X	* Article on the bactericidal effects of silver (1f).
Dhanoa 2015 [1]	Retrospective cohort 2007–2011	N = 105 Endoprosthetic reconstruction for tumor	* 54% DAIR * 46% 2-SR	32 months	* 12.4% infection at 0-63 months. * Higher risk after additional procedures (13x), comorbidity, proximal tibia endoprostheses, pelvic endoprostheses and preoperative hospitalization >48 hour. Lower risk with distal femoral prostheses. * 80% of infections had operations >2.5h, compared to 16.3% in non-infections. * 38% Staph aureus, 31% CNS, 23% Klebsiella pneumoniae, 23% Pseudomonas aeruginosa. 38.5% had polymicrobial infection (1d). * 80% of 2-SR were successful; 1 patient had antibiotic suppression. * 43% of DAIR were successful; 2 patients had antibiotics; 2 patients had amputation (2).
Donati 2016 [19]	Retrospective case-control 2005–2016	N = 68 Megaprosthesis reconstruction for proximal femur tumors	X	47 months (12-114 months)	* Overall infection rate 11.8% at mean 25 months: silver 7.9%, control 16.7% (1f). * In late infection, explanted megaprostheses had important degradation of the coating surface (1f). * No differences in functional scores between silver and control (1f). * No local or general signs of toxicity (1f).
Felden 2015 [20]	Prospective cohort 1995–2011	N = 45 Pelvic irradiation before cemented THA	X	51 months (17-137 months)	* Patient survival was 71% at 2y, 52% at 5y and 41% at 10y. * The cumulative probability of revision was 2.2% at 1y, 2.2% at 2y, 8.1% at 5y and 20.2% at 10y. * 6% underwent revision for infection, 1 treated with 2-SR, 2 treated with 1-SR (all successful).
Flint 2007 [2]	Prospective cohort 1989–2004	N = 15 Infection after uncemented Kotz prostheses for bone sarcoma	2-SR	42 months (3-150 months)	* Prosthetic infection occurred at mean 28 months (1-132 months). * 75% CNS, 33% Staph aureus, 8% Pseudomonas aeruginosa, 8% E. coli, 8% Streptococcus viridans (1d). * 73% had second-stage revision: 27% had amputation, 73% with infection control after second-stage. * 60% success with retention of diaphyseal stems; 40% success with removal of anchorage pieces. * No relation between success and anatomical location or infecting organism (1d). * 66% of failures had previous radiation (1c). * In case of infection within 6 months 86% of 2-SR was successful, after 6 months only 25%.

TABLE 2. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Funovics 2011 [7]	Retrospective cohort 1982–2008	N = 166 Endoprosthetic reconstruction for tumor	* 83% 1-SR * 8% muscle flap * 8% deceased	47 months (0-365 months)	* Survival rate without infection was 95.9% at 1y, 89.2% at 5y, 89.2% at 10y and 77.8% at 20y. * 7.2% had infection at mean 39 months (0-167 months). * 30% CNS, 30% Staph epidermidis. Polymicrobial infection in 30.8% (1d). * Higher rate of infection in primary tumors, cemented prostheses, pelvic reconstruction, additional operations or radiotherapy (1c). * 63% infection control by 1-SR, 13% additional 1-SR, 25% additional 2-SR.
Gitelis 2008 [21]	No full text	X	X	X	X
Grimer 2002 [3]	Prospective cohort 1989–1998	N = 34 Infection after endoprostheses for sarcoma	2-SR	6-116 months	* Obvious causes of infection included lengthening or rebushing procedures, infected ingrown toenail, chest infection, infected burn blister, infected Hickman catheter and neutropenic septicaemia. * 53% CNS, 32% Staph aureus, 6% streptococci, 3% Enterobacter and 3% Corynebacterium (1d). * 70% had infection control after 2-SR. 6% needed amputation within 6 months. 6% needed additional 2-SR (1 successful, 1 not). 18% had late infections with various treatments. * Overall success rate for controlling infection was 94% at 6 months, 91% at 1 year, 74% at 5 years and 65% at 10 years. * Reinfection occurred in all 3 patients with previous radiotherapy (1c). * Functional outcome after successful infection control was mean 77% MSTS (47-100%).
Hardes 2006 [8]	Retrospective cohort 1992–2003	N = 30 Infection after MUTARS tumor endoprostheses for sarcoma	* 3.3% antibiotics * 10% 1-SR * 80% 2-SR	32 months (3-128 months)	* Infection occurred at mean time 16 months (1-70 months). * 62% CNS, 21% Staph aureus, 14% Enterococcus species. 21% had polymicrobial infections (1d). * 1-SR was successful in 33%, 2-SR in 63% * 33% of 2-SR failures needed amputation, 33% rotationarthroplasty, 11% arthrodesis, 22% retained the spacer (1 died after 4 months, 1 had satisfactory function). * 8.3% needed a change of spacer (1f). * The most important risk factor for failed limb salvage was poor soft tissue. * Chemotherapy, time of occurrence of infection, virulence and type of infection had no influence (1b). * A mean of 2.6 revision operations per patients, mean duration of hospital stay 68 days.

TABLE 2. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Hardes 2007 [22]	Prospective cohort 2002–2004	N = 20 Silver-coated MUTARS tumor endoprostheses for metastasis	X	19 months (2-32 months)	* No patients had signs of local or systemic argyrosis (1f). * The mean serum silver concentration was 0.37 ppb preoperatively, 2.80 ppb 2 week postoperatively. Between 2 and 24 months silver concentration varied from 1.93 – 12.98 ppb (1f). * 10 patients showed decreased glomerular filtration rates (1f). * The silver-coating was intact in all patients. Histologic examination showed no signs of chronic inflammation, granulomas or necrotic tissue (1f).
Hardes 2010 [23]	Prospective case-control 2005–2009	N = 51 (74 control) Silver-coated replacement for bone or soft-tissue tumors	Various	19 months (3-63 months)	* 5.9% with silver had infections compared to 17.6% with titanium prostheses, at mean 11 months (1f). * Patients with infection had longer operating time (305 vs. 228 minutes). * 38.5% with titanium prostheses had amputation or rotationplasty for infection, 0% in silver group (1f). * In the silver group 2 were treated with antibiotics alone, 1 had minor revision (one-stage without removal of the stem), all were successful (1f).
Henderson 2011 [24]	Retrospective cohort 1974–2008	N = 2,174 Limb preservation with metallic endoprostheses for tumor	X	X	* 24.5% were considered failures, of which 12% had soft tissue problems, 19% aseptic loosening, 17% fracture, 17% tumor progression, 34% infection. * Infection occurred more often in hinged prostheses than in polyaxial protheses ($p < 0.05$). * Failure incidence decreased over time. The mean time to failure was 47 months. * Literature review of 4359 patients with 29% failures.
Hollinger 1996 [25]	No full text	X	X	X	X
Hsu 1999 [26]	Prospective cohort 1975–1986	N = 38 Limb salvage for tumors needing revision surgery	* 50% revision * 32% amputation * 10% arthrodesis * 8% miscellaneous	51 months	* Indications for reoperation were aseptic loosening (34%), instability (13%), infection (13%), tumor recurrence (13%), fracture (11%) and miscellaneous (16%). * 16% died after revision at a mean of 40 months after revision. * After revision functional results were excellent (12.5%), good (81.3%) or fair (6.25%). * 63% had radiolucent zones immediately after revision. 25% of these developed progressive changes that had an effect on limb function. * Patients with revision had higher survival rates and longer disease-free intervals than patients with amputation ($p < 0.01$). * Overall 18.4% had complications: 5.3% aseptic loosening, 5.3% infection, 2.6% non-union, 2.6% local recurrence and 2.6% instability.
Jacobs 1995 [27]	Retrospective cohort 1983–1991	N = 9 Uncemented THA with previous pelvic irradiation	X	37 months (17-78 months)	* 4/9 radiographic and clinical migrations, 2/4 had revision, of which 1 needed Girdlestone after revision (1c).

TABLE 2. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Jeys 2003 [28]	Retrospective cohort 1966–2001	N = 1,261 Endoprostetic replacement	Amputation	5.2 years	* Overall patient survival was 60% at 5 years, 54% at 10 years and 40% at 20 years. * Overall limb survival without amputation was excellent with 91% at 20 years. * Overall risk of amputation was 8.9% of which the reasons were local recurrence (63%), infection (34%), mechanical failure (2%) and persistent pain (1%). * Risk of amputation after infection was 19% compared to 36% for local recurrence. * Time to amputation was a mean of 32 months for infection.
Jeys 2005 [4]	Retrospective cohort 1966–2001	N = 1,240 Prosthetic replacement for bone tumor	* 43% 2-SR * 32% amputation * 24% 1-SR * 2% Girdlestone	5.8 years (0.3-34 years)	* 11% had infection from 1996-2001 3.7%, 14% from 1966-1996. * 88% presented within 2 years after the last surgical procedure. * 48% had Staphylococcus epidermidis, 26% had polymicrobial infection (1d). * Polymicrobial infections did not reduce the rate of successful treatment of infection (1d). * Success rates: amputation 98%, 2-SR 72%, Girdlestone 50%, 1-SR 42%.
Jeys 2007 [29]	Retrospective cohort 1966–2001	N = 412 Endoprosthetic reconstruction for osteosarcoma	X	6.7 years (0-20 years)	* 10% had deep infection at mean time 4.6 months. * 52% had Staph epidermidis, 29% Staph aureus (1d). * There was better survival in patients infected with Staphylococcus (10y survival 92%, mixed organisms 79%, no infection 62.2%, Streptococcus 50%) (1d) * There was no evidence that patients with infections had more effective chemotherapy (1b) * There were more infections after radiotherapy (p=0.02) (1c)
Jeys 2007 [30]	Retrospective cohort 1966–2001	N = 1,254 63 radiotherapy Endoprosthetic replacement for bone tumor	X	5.8 years (0.3-33 years)	* Mean postoperative MSTS function score was lower after radiotherapy (64% vs. 81.3%) (1c) * Risk of infection without radiotherapy 9.8%, preoperative radiotherapy 20.7%, postoperative radiotherapy 35.3% (1c). * Risk of amputation without radiotherapy 7.8%, preoparative radiotherapy 17.2%, postoperative radiotherapy 14.7% (1c). * 10y survival was worse after radiotherapy (29%) than without radiotherapy (58%) (1c).
Jeys 2009 [31]	No full text (chapter book)	X	X	X	X
Kaminsky 2017 [32]	No full text	X	X	X	X
Kim 2007 [33]	Prospective cohort 1997–2003	N = 51 Uncemented THA with irradiation of the pelvis for adenocarcinoma of the prostate	X	4.8 years (2-7.5 years)	* 47% had radiation induced osteonecrosis of the femoral head (1c). * 6% had wound discharge, which healed without surgical treatment (1c). * 2% had deep infection, which required subsequent resection arthroplasty (successful) (1c).

TABLE 2. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Lansdown 2010 [34]	Narrative review	X	X	X	* Paper about the mechanisms of absorption and metabolism of silver in the human body, presumed mechanisms of argyria and the elimination of silver-protein complexes in the bile and urine (1f). * Argyria and argyrosis are the principle effects associated with heavy deposition of insoluble silver precipitates in the dermis and cornea/conjunctiva. Argyria is not associated with pathological damage (1f).
Lee 2002 [5]	Retrospective cohort 1985–1998	N = 145 18 infection Tumor prosthesis for bone and soft tissue tumors	* 78% DAIR * 11% 2-SR * 11% 1-SR	44 months (5-136 months)	* 12.4% had infection at mean 8 months (0.5-54 months). * 39% was successfully treated with DAIR or revision; 17% needed arthrodesis and 11% amputation (2). * 100% of 2-SR were successful, 0% of 1-SR were successful. * 33% with uncontrolled infection by DAIR and refused prosthesis removal had suppressive antibiotics. * The knee joint seemed to show poor outcome, but this was not statistically meaningful. * Infection control was poor in cases of cementless fixation ($p < 0.01$). * Chemotherapy gave a higher risk of infection (18.7% vs. 5.6%) (1b). * Soft tissue defects (sinus, pus discharge, wound dehiscence) correlated with poor prognosis ($p < 0.05$).
Li 2011 [35]	Retrospective cohort 1993–2008	N = 53 Endoprosthetic reconstruction for sarcoma	DAIR	10 years	* 1.9% had early infection, successfully treated with DAIR (2). * 5.7% had late infections, all treated with DAIR. One was successful, 2 needed revision (successful) (2). * 7.5% had wound complications requiring repeat surgery (debridement and closure) (2).
Manoso 2006 [16]	Retrospective cohort 1990–2001	N = 11 Infected knee reconstruction after limb-salvage surgery for cancer treated with staged protocol	Staged reconstruction protocol	X	* 82% had chronic infection, with a sinus tract in 45% at mean time 6 months (1-210 months). * 45% had failed DAIRs (2). * 55% had Staph aureus, 27% had Staph epidermidis. In 55%, a single organism caused the infection (1d). * 82% were immunocompromised with the administration of chemotherapy at the time of infection (1b). * All limbs were spared without amputation or flap loss. Overall cure rate was 91%. * Early complications were 2 peroneal palsies and 1 venous flap congestion requiring wound revision. * The mean functional outcome was 23/30 and mean knee range of motion 98 degrees.
Massin 1995 [36]	Excluded	X	X	X	X

TABLE 2. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Mavrogenis 2015 [37]	Retrospective cohort 1983–2010	N = 1,161 Megaprosthesis reconstruction after limb salvage surgery for sarcoma	* 83% 2-SR * 12% 1-SR * 5% amputation	Mean 9 years (3-20 years)	* 8.6% had infection at mean time 3.7y. * Most common isolates were Staph epidermidis (47%), Staph aureus (19%) and pseudomonas (6%) (1d). * Overall survival rate of megaprostheses was 88% at 10y and 84% at 20y. * Survival was higher for cementless reconstruction, not different for type of megaprosthesis, site of reconstruction or adjuvant therapy (1b).
Mavrogenis 2011 [38]	Narrative review	X	X	X	* DAIR may be effective in early infections, with short duration of symptoms, well-fixed implants and ideally with well-characterized microbiology demonstrating a highly susceptible pathogen (2). * Success in 2-SR 72-91%, 1-SR 42% and amputation 98-100%. * 2-SR is recommended for persistent infections, antibiotic-resistant pathogens or failed 1-SR. In well-fixed cementless modular prostheses anchorage stems can be retained. * Disadvantages of 2-SR are long hospitalization, increased bone loss, disuse osteoporosis, difficult revision operations and shortening of the affected limb. * Reimplantation should be delayed after completion of chemotherapy (1b). * An antibiotic-loaded cement spacer is essential in 2-SR; added antibiotics should be heatstable (1e). * Most surgeons administer systemic antibiotics 6 weeks, with reimplantation after > 2 months (1a).
McDonald 1990 [39]	Retrospective cohort 1970–1986	N = 304 271 malignant 33 benign Prosthesis or non-biological spacer in limb salvage surgery for primary bone tumors	X	2 years	* 11.8% had infection, 22% of these patients needed amputation. * Adjuvant and neo-adjuvant chemotherapy gave a higher risk of complications (32.8% and 55.4% vs 25.2%). Reconstruction with uncemented prostheses had fewest complications (1b).
Mittermayer 2002 [40]	Excluded	X	X	X	X
Morii 2010 [41]	Retrospective cohort 2000–2008	N = 82 Endoprosthetic reconstruction for knee tumors	X	52 months (9-105 months)	* 17% had infection at mean time 10.9 months. * 50% had Staph aureus, 30% Staph epidermidis and 10% Pseudomonas (1d). * Age, sex, tumor origin, comorbidities, operating time, blood loss, chemotherapy, clean air operating room, extracapsular resection, prosthesis type, number of postoperative antibiotics, posterior muscle flap were not risk factors for infection (1b). * Skin necrosis and surface infection were risk factors for infection.

TABLE 2. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Morii 2013 [6]	Retrospective cohort 1995–2009	N = 388 Endoprosthetic reconstruction for knee tumors	* 45% debridement * 14% 2-SR * 10% amputation * 9% 1-SR * 7% soft tissue flap	66 months (5-213 months)	* 14.6% had infection at mean time 13 months. * 47% Staph aureus and 17.5% Staph epidermidis (1d). * Infections were controlled in 84.2% the others had an accepted fistula or suppressive antibiotics. * Patients with diabetes, bone metastasis, lack of gastrocnemius flap coverage and pus required more surgical interventions for infection control. * The most successful therapy was 2-SR (80% success). Therapies with prosthesis removal were more successful than other therapies.
Peel 2014 [9]	Retrospective cohort 1996–2010	N = 121 Tumor endoprostheses surgery	* 53% DAIR * 24% 2-SR * 12% 1-SR * 6% resection * 6% amputation	34 months (17-80 months)	* 14% had infection at median time 18 months * Parenteral antibiotics median 9 days (0-58), 82% received oral combination antibiotic therapy with rifampicin (365 days) (1a). * Success rates: DAIR 75%, 1-SR 100%, 2-SR 50%, resection 0%, amputation 100% (2). * The majority of treatment failures occurred in patients with multi-resistant organisms (1d).
Pilge 2012 [42]	No full text	X	X	X	X
Racano 2013 [43]	Systematic review 1990–2011	N = 4,838 in 48 level IV studies	X	X	* Pooled infection rate was 10% (0-25%). * Most common organisms were Staph aureus and Staph epidermidis (1d). * There is considerable variation in antibiotic regimens. 0-24 hour antibiotic prophylaxis had 13% infection, >24 hour prophylaxis had 8% infection ($p<0.05$) (1a).
Renard 2000 [44]	Prospective cohort 1975–1995	N = 77 Limb saving surgery (50) or ablative surgery (25) for sarcoma	X	97 months (28-271 months)	* 6% had deep infection, leading to amputation in 2/3 cases. * 4% had superficial infection successfully treated with DAIR and gentamicin beads (2).
Sherman 2008 [45]	Excluded	X	X	X	X
Shin 1999 [46]	Retrospective cohort 1970–1990	N = 52 41 malignant 11 benign Limb salvage surgery for musculoskeletal tumor	* 67% revision * 21% amputation * 8% arthrodesis * 2% fibular graft * 2% ORIF	12 years (37-296 months)	* 11.5% had infection. * Functional rating was 63%. Pain 69%, function 53%, emotional acceptance 72%, support 60%, walking ability 62%, gait 54%, hand positioning 66%, manual dexterity 94% and lifting ability 63%. * After revision 33% needed reoperation for complications: 58% aseptic loosening, 25% infection, 17% prosthetic failure and 8% patellar dislocation. * Survival after reoperation was 79% (5y) and 65% (10y).

TABLE 2. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Sim 2007 [47]	Retrospective cohort 1996 – 2005	N = 50 Endoprosthetic reconstruction for knee tumors (GRMS)	3 washouts	24.5 months (2-124 months)	* Patients with metastatic disease or pathological fractures did not have higher complication rates. * 12% had deep infection for which patients received multiple washouts and long-term antibiotics (2). * 1/6 had revision; 1/6 had amputation (2).
Wafa 2015 [48]	Prospective case-control 2006–2011	N = 170 Reconstruction with silver-enhanced endoprostheses for several indications	X	12 months	* 11.8% infection in silver group, 22.4% in control group (1f). * Higher incidence of Pseudomonas in the silver group (1d/1f). * 70% of infected prosthesis was successfully treated with DAIR, 31.6% in the control group (1f/2). * 15.3% required implant removal, amputation or antibiotic suppression, 3.5% in the silver group (1f). * 18.8% with adjuvant chemotherapy developed infection (1b). * 15% had relapse infection after 2-SR in the silver group, 42.9% in the control group (1f).
Wirgano-wicz 1999 [49]	Prospective cohort 1980–1995	N = 64 Failed endoprostheses for neoplastic disease	* 75% revision * 25% amputation	2 years	* 13% failed because of an infection. * 50% of infected prostheses had revision with the same prosthesis, 25% with a different prosthesis and 25% underwent amputation. * Patients receiving revision endoprostheses were not at increased risk for a subsequent revision or amputation compared to primary endoprostheses reconstruction.
Zajonz 2016 [50]	Retrospective cohort 1994–2014 Excluded	N = 34 Modular endopros-theses of the lower extremity for infection	X	72 months (6-267 months)	* Reinfection rate after healed reinfection in silver group was 40%, in the non-silver group 57% (1f).
Zajonz 2017 [51]	Retrospective cohort 1994–2011	N = 101 45 tumor Modular endoprostheses of the lower extremity	* 62% 2-SR * 11% resection * 11% arthrodesis * 8% DAIR * 8% amputation	27 months (5-179 months)	* 17.7% had infection (3 early infections, 16 late infections), reinfection rate 37%. * 36.6% CNS, 26.3% Staph epidermidis, 15.8% Staph aureus (1d). * Patients with infection had same age and sex, but higher BMI. * Prosthesis for tumors had fewer infections than other indications (8.9% vs. 21.7%).

of strong levels of evidence published in the form of meta-analyses or randomized controlled trials, we compiled a narrative review discussing various factors associated with infection control in oncologic endoprostheses.

Search Strategy

A literature search was performed in PubMed with relevant search terms on the 23rd of January 2018. The literature search resulted in 83 hits. Additional articles for screening were selected from the reference lists. Articles that were not written in English or did not have full text available were excluded. Twenty-nine articles were excluded based on title and abstract. Another 4 articles were excluded after thorough reading of the full text articles, whereby we included 41 articles in our literature analysis (see Tables 3 and 4).

DAIR procedure is one of the treatment approaches described for PJI of endoprostheses in cancer patients. However, treatment outcomes after DAIR are very variable and unpredictable in an oncology setting. Success rates vary between 39-70% [1,9–12]. Some of the reported factors that are associated with better outcomes after DAIR include superficial early infection, short duration of symptoms, well-fixed implants and well-characterized microbiology demonstrating a highly susceptible pathogen [13–15]. Unfortunately, the studies that reported on DAIR outcomes have very variable periods of clinical follow-up (34 months –10 years).

The most common microorganisms causing infection of oncological endoprostheses are *Staphylococcus aureus* and coagulase negative staphylococci, both account for > 50% of PJI. A large number of the documented infections were also polymicrobial infections accounting for 21-45% of cases [1,4,7,8,16]. There was no difference between monomicrobial and polymicrobial infections regarding outcome [4]. A study by Peel et al. was the only report demonstrating that the majority of infections of endoprosthesis were caused by multi-resistant microorganisms [9]. In one study, the success of outcome for DAIR as well as for two-stage revision for PJI of endoprosthesis did not show any correlation with the infecting organism [2]. It is important to note that the aforementioned results are based on a small number of patients, making generalizability of the findings somewhat limited.

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TABLE 3. Exclusion after reading full text article

Author and Year	Reason for Exclusion
Massin, 1995 [36]	No tumorprosthesis, radiation followed by reconstruction with normal prosthesis, 2 late infections (2yr) of 71 cases, both girdlestone
Mittermayer, 2002 [40]	No information on infection, only on aseptic revision in retrospective cohort
Sherman, 2008 [45]	Case report
Zajonz, 2016 [50]	No tumorprostheses, only modular endoprostheses after PJI

TABLE 4. Exclusion after screening abstract and title

Author and Year	Reason for Exclusion
Aponte-Tinao, 2016 [52]	Does not answer the research question
Ascherl, 2010 [53]	Article in German language
Baker, 2011 [54]	Does not answer the research question
Bielack, 1999 [55]	Article in German language
Bosetti, 2002 [56]	Does not answer the research question
Brigman, 2003 [57]	Does not answer the research question
Buttaro, 2005 [58]	Does not answer the research question
Cho, 2005 [59]	Does not answer the research question
Deelstra, 2013 [60]	Does not answer the research question
Dieckmann, 2014 [61]	Does not answer the research question
Falkinstein, 2008 [62]	Does not answer the research question
Foo, 2011 [63]	Does not answer the research question
Gebert, 2010 [64]	Does not answer the research question
Glehr, 2013 [65]	Does not answer the research question
Gooding, 2011 [66]	Does not answer the research question
Gosheger, 2004 [67]	Does not answer the research question
Goulding, 2017 [68]	Does not answer the research question
Hillmann, 2000 [69]	Does not answer the research question
Ji, 2012 [70]	Article in Chinese language
Kühne, 2003 [71]	Does not answer the research question
Lautenschlager, 1976 [72]	Does not answer the research question
MacMull, 2010 [73]	Does not answer the research question
Mäkinen, 2017 [74]	Does not answer the research question
Malhotra, 2012 [75]	Does not answer the research question
Meek, 2004 [76]	Does not answer the research question
Nazar, 1999 [77]	Article in Polish language
Nebelung, 2000 [78]	Does not answer the research question
Niculescu, 2008 [79]	Does not answer the research question
Nobile, 2015 [80]	Article in Italian language
Pala, 2017 [81]	Does not answer the research question
Radunovic, 2016 [82]	Does not answer the research question
Schmolders, 2017 [83]	Article in German language
Sudmann, 1994 [84]	Does not answer the research question
Vcelak, 2017 [85]	Article in Czech language
Wang, 2011 [86]	Article in Chinese language
Wicart, 2002 [87]	Does not answer the research question
Wilding, 2016 [88]	Does not answer the research question
Wise, 1990 [89]	Does not answer the research question
Yoshida, 2010 [90]	Does not answer the research question

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2.2. TREATMENT: ONE-STAGE EXCHANGE

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QUESTION 1: Does the use of iodine-coated or silver-coated implants make one-stage exchange arthroplasty possible in the management of patients with infected oncologic endoprosthesis?

RECOMMENDATION: Unknown. Current literature has advocated the advantages of surface-modified coating (e.g., silver-coated, iodine-supported implants). Recently, there have been several low-quality, small-scale studies showing promising results for using surface-modified implants in one-stage exchange arthroplasty to treat infected oncologic endoprosthesis. However, to date there remains unsubstantiated evidence and large-scale, high-level evidence studies are necessitated.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The basic treatment for malignant musculoskeletal tumors is a combination of surgical treatment with adjuvant radiation and chemotherapy. Specifically, limb salvage surgery is becoming the standard treatment for oncologic patients, because the effectiveness of chemotherapy has immensely improved in recent decades [1]. Prosthetic reconstruction using an endoprosthesis provides the best possible level of functionality in patients who require a wide excision for a malignant bone or soft tissue tumor because of improved surgical techniques and implant devices. However, periprosthetic joint infection (PJI) continues to be a serious complication after the placement of an endoprosthesis and is not uncommon to observe [2]. Prior literature has demonstrated that the infection rate of an endoprosthesis ranged from 4-36% [3–6]. Therefore, prevention of PJI becomes an essential task for success, particularly in this patient population. An increasingly popular method used in preventing PJI is the utilization of surface-modified implants with antimicrobial effects, such as iodine-coated or silver-coated implants.

Silver has been widely investigated because of its strong broad-spectrum antibacterial properties, anti-biofilm potential and low cytotoxicity [7–11]. Currently, there are several case series and a few case control studies that examine the success of one-stage revision arthroplasty using silver-coated implants for infected oncologic endoprostheses [12–17]. In a case series of four infected endoprostheses, Zajonz et al. demonstrated that one-stage revision arthroplasty resulted in no subsequent reinfection of the endoprostheses [17]. Wafa et al. [16] conducted a case-control study comparing outcomes for silver-coated prosthesis versus unmodified prosthesis in oncologic patients. In terms of single-stage revisions, they noted a lower rate of infection in the silver group compared to the control group, although this was not statistically significant (5.1% vs. 12.5%; $p = 0.249$). There was, however, a marginally significant decrease in infection rate for two-stage revisions with silver-coated implants (15% vs. 42.9%; $p = 0.05$). Hardes et al. reported that patients who initially underwent placement of a silver-coated prosthesis ($n = 51$) had reduced total infection rates [13]. In addition, the infections that did develop required less aggressive treatment compared to the titanium implant control group ($n = 74$). Similar findings were later produced by the same team for endoprostheses involving the proximal tibia in patients with sarcoma [18].

Iodine-supported implants also exemplify strong inhibition of biofilm formation by preventing antibacterial attachment on metal surfaces similar to silver-coated implants [19–21]. There are three clinical reports that suggest the effectiveness of iodine-supported implants for patients with malignant bone or soft-tissue tumor [19–22]. Shira et al. showed that both one-stage ($n = 11$) and two-stage ($n = 15$) exchange arthroplasty with iodine-supported implants were sufficient to treat infection without need for additional surgery in all cases [19]. However, it is noted that one-stage revision surgery was employed for inactive or quiescent infections and two-stage revision surgery was indicated for active infections (defined by "active sinus discharge or abscess formation or C-reactive protein (CRP) > 0.5 mg/dl"). Nevertheless, there is a need for prospective case-control studies or randomized controlled trials investigating the use of iodine-supported implants in one-stage revision arthroplasty.

In conclusion, it is uncertain whether silver- or iodine-modified implants are effective for one-stage revision arthroplasty in infected oncologic endoprosthesis based on limited literature. There are a few studies in circulation that are promising and advocate for their success in one-stage revision surgery for eradicating infection. This investigative team believes that additional larger-scale investigations involving randomized control trials, prospective cohort and case-control studies are warranted.

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QUESTION 2: Is there a role for single-stage exchange arthroplasty for patients with infected oncologic endoprosthesis?

RECOMMENDATION: In principle, despite the lack of sufficient evidence, single-stage exchange arthroplasty can be performed in patients with infected oncologic endoprosthesis if the general requirements to perform a single-stage procedure are fulfilled. However, a single-stage revision without removing the anchorage components is not recommended, since better infection control can be achieved when prostheses were removed rather than salvaged.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Periprosthetic joint infections (PJIs) are serious complications of reconstruction of defects created by tumor resection. The reconstruction in tumor surgery usually involves the use of modular endoprostheses. Infection following tumor surgery and reconstruction is relatively common, occurring in 8 to 35% of primary implants [1–3]. As limb salvage surgery has gained popularity over the recent years, the number of reconstruction procedures after tumor resection, and the ensuing infections, have increased [1–3].

Despite the high incidence of PJI following oncologic reconstruction, and perhaps because of the relatively low volume of tumor reconstruction cases, there is a universal lack of high-quality studies related to PJI following oncologic reconstructions. The review of current available literature reveals only 12 relevant articles on infections following oncologic reconstructions using tumor endoprostheses. Only six published articles reported the outcomes of single-stage exchange arthroplasty [2,4–8]. However, it must be noted that some of the authors perform a single-stage revision with removal of all exchangeable and polyethylene components with debridement of surrounding soft tissues but without removal of the fixation anchoring components [2,4–8].

As presented by Buchholz et al. in the 1970s, the concept of classic single-stage exchange arthroplasty after infected total joint replacement is the radical debridement and removal of all foreign materials [9]. Morii et al. found that infection control rates were significantly higher when prostheses were removed rather than salvaged in a series of 57 patients with PJI of tumor endoprostheses [4]. According to Hardes et al., an optimal soft tissue condition is imperative for a successful limb salvage procedure [7].

Currently, there is no concrete evidence in the literature to answer the question, "What role, if any, does one-stage exchange arthroplasty play in the management of PJI after oncologic reconstruction using modular endoprostheses?" However, borrowing from the hip and knee adult reconstruction literature, one can state that the rate of infection control is usually better when all prosthetic and foreign material are removed and new implants used either at the same time (one-stage exchange) or at a later date. It is also an agreed principle that the rate of infection control correlates with the extent of debridement and bioburden reduction. Applying these principles, we can state that one-stage exchange arthroplasty does have a role in the management of acute or chronic PJI following oncologic reconstruction. The question that remains and is somewhat unique to oncologic reconstruction is whether all foreign material needs to be removed during one-stage exchange or some parts, such as the anchoring portion of the prosthesis in the bone, can be retained. The tendency would be to advocate that all foreign material should be removed during one-stage exchange. However, removal of the anchoring part of the prosthesis may not be possible or removal of this part may preclude a later reconstruction. Under these circumstances, sub-radical resection arthroplasty may be performed. It is critical, however, that the retained prosthesis is cleaned physi-

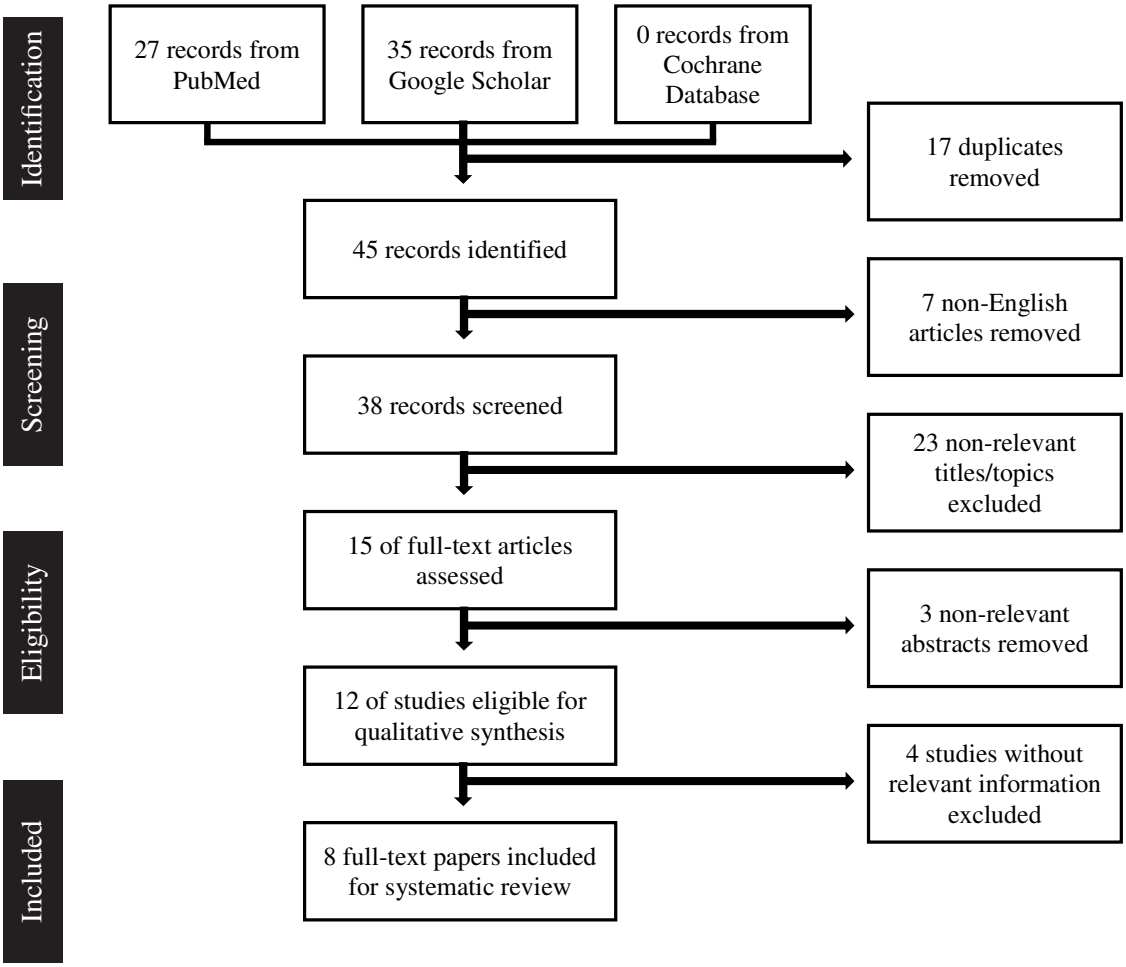

FIGURE 1. PRISMA Flowchart showing the identification of relevant studies during the review process.

cally and chemically with agents such as chlorhexidine or povodine iodine scrubs and washed thoroughly. Obeying the general principle of infection surgery is likely to allow some patients with infected oncologic prostheses to be treated by one-stage exchange arthroplasty. Future research is needed to determine which group of patients would most benefit from one-stage exchange arthroplasty versus two-stage exchange arthroplasty.

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2.3. TREATMENT: RESEARCH CAVEATS

Authors: Germán Luis Farfalli, Peter Choong, Sam Francis

QUESTION 1: Should the management of periprosthetic joint infection (PJI) involving an oncologic endoprosthesis differ from that of conventional joint replacement prostheses?

RECOMMENDATION: No. The management of PJI involving an oncologic endoprosthesis is similar to that of conventional joint replacement prosthesis.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Deep infection of primary total joint arthroplasty (TJA) is a catastrophic complication. However, the infection rate is relatively low [1]. Tumor endoprosthesis are essentially larger implants similar to those used in total joint replacements, although the type of surgery and the risk factors related to the type of patient differ significantly [2,3]. Therefore, a deep infection with these types of implants drastically worsens the prognosis of the affected limb and significantly increases the risk of amputation compared to conventional prosthetic arthroplasties [2,3].

Despite these differences in the rate of complications between primary arthroplasties and endoprostheses, the management of postoperative infections is similar. There is a general consensus that infections are divided into either early or late infections, according to the time of diagnosis [4–9].

Despite the large amount of literature analyzing PJIs, there are no comparative studies between management and outcomes nor between primary prostheses and endoprosthesis. There are only a limited number of retrospective studies focused on the outcomes of periprosthetic infections in endoprostheses [10–13]. Therefore, the management of infections in endoprostheses is based on protocols used in primary prostheses. A new strategy that seems to be improving the results at the time of endoprostheses re-implant is silver-coated endoprostheses. Wafa et al. [14] suggests in a retrospective case-control study that the overall success rates in controlling infection by two-stage revision in patients treated with silver-coated endoprosthesis was 85%, compared to uncoated tumor prostheses ($p = 0.05$, Chi-square test). The Agluna-treated endoprostheses were associated with a lower rate of early periprosthetic infection. In addition, these silver-treated implants were particularly useful in two-stage revisions for infection and in those patients with incidental positive cultures at the time of implantation of the prosthesis. Finally, they conclude that debridement with antibiotic treatment and retention of the implant appeared to be more successful with silver-coated implants.

There is no consensus in the management of an infected endoprosthesis given the limited data. The current recommendation is based on treatment of infected primary arthroplasties.

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2.4. TREATMENT: TWO-STAGE EXCHANGE

Authors: Paul Jutte, Hesham Abdelbary, Claudia Löwik

QUESTION 1: What factors may improve the outcome of a two-stage exchange arthroplasty in patients with an infected oncologic endoprosthesis?

RECOMMENDATION: There are numerous factors that improve the outcome of two-stage exchange arthroplasty in general, and after oncologic reconstruction in particular. These include host-related factors (such as host optimization by treating anaemia, malnutrition, hyperglycemia, immunosuppressive state and so on), organism-related factors (such as administration of appropriate systemic and local antibiotics) and surgery-related factors (such as aggressive debridement of soft tissue and bone, optimal soft tissue management and prevention of postoperative complications).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Surgical reconstruction using a mega-endoprosthesis after tumor resection can be frequently associated with deep surgical site infection that leads to prosthetic joint infection (PJI). The prevalence of PJI associated with oncologic endoprosthesis is 7-28% compared to only 1-2% in primary joint replacements. Cancer patients are at a higher risk for developing PJI after receiving an endoprosthesis due to numerous risk factors, which lead to local and systemic immunodeficiency. These risk factors include chemotherapy, radiotherapy, prolonged surgical time, increased bleeding, larger implant surface area and compromised soft tissue envelope.

In case of an infected oncologic endoprosthesis, debridement, antibiotics and implant retention (DAIR) can be performed, especially in early acute infections (< 3 months). If DAIR fails to eradicate the infection, a two-stage revision is necessary. In literature, two-stage revision is generally reported as a good surgical approach for infection control with a reported success rate of 63-100% [1–6]. Eradication of infection is generally worse after a single-stage revision and, of course, better after an amputation [4,7–9].

Although various studies assessed infection after oncologic endoprostheses, only a few have specifically evaluated the efficacy of DAIR or two-stage revision [2,3]. The factors associated with infection control in oncologic endoprostheses have been individually discussed. After review of the literature, 41 articles were included in our literature analysis. The most important study characteristics are described in the evidence table.

Antibiotics

Little is known about the use of antibiotics in two-stage revision for an infected oncologic endoprostheses. In all studies, antibiotic regimens differed per patient according to culture results and local protocol without specific details being provided. In general, antibiotics should be administered for three months, and the type of antibiotics is decided based on culture results, as well as the consultation with an infectious disease specialist. There are no studies stating that administering antibiotics longer than three months is necessary. Regarding antibiotic prophylaxis, it is recommended to administer prophylactic antibiotics for more than 24 hours, since a systematic review of Racano et al. showed that this reduces the infection rate from 13% to 8% [10]. Regarding the timing for reimplantation after PJI treatment, there is no evidence for the optimal timing other than waiting for completion of chemotherapy before reimplantation [11].

Chemotherapy

The influence of chemotherapy can be expected since it down regulates the host defence mechanisms. However, this is not uniformly reported in the assessed studies. Several studies found an increased risk of developing an infection after implantation of an oncologic endoprostheses in patients undergoing chemotherapy [5,11,12]. However, other studies did not confirm this notion [8,13,14]. Because of the immunocompromised status of patients receiving chemotherapy, it is advised to delay reimplantation until after completion of chemotherapy [15].

Radiotherapy

Application of radiotherapy increases the risk of infection after oncologic endoprosthesis [7,16]. Grimer et al. and Flint et al. found a higher failure rate in patients who underwent radiotherapy [2,3]. Regarding timing of radiotherapy, postoperative radiation has a bigger influence on the infection rate than preoperative radiotherapy [16]. The success rate of DAIR procedures in which postoperative radiotherapy had been applied was lower. Radiation influences the quality of soft tissue and hampers local defence mechanisms.

Microorganisms

The most common microorganisms causing infection of oncological endoprostheses are *Staphylococcus aureus* and coagulase negative staphylococci that account for > 50% of PJI. Many of the documented infections were also polymicrobial infection accounting 21-45% of cases [1,4,7,8,17]. There was no difference between monomicrobial and polymicrobial infections regarding cure rate [4]. A study by Peel et al. demonstrated that the majority of infections were caused by multi-resistant microorganisms [9]. Cure rates for DAIR as well as for two-stage revision after PJI did not show any correlation between the infecting organism and the success of eradicating the infection [2]. It is important to note that the aforementioned results are based on a small number of patients. Therefore, it is difficult to draw firm conclusions that can be generalized to all cases of infection associated with oncologic endoprostheses.

Silver-coated Arthroplasty

Few studies have reported on the benefits of using silver-coated endoprostheses to decrease the risk of developing PJI in patients

treated for primary and metastatic bone cancer. Silver cations possess bactericidal properties by disrupting cellular membrane and DNA formation. Donati et al. and Wafa et al. reported a 50% less incidence of PJI in patients treated with silver-coated megaprosthesis compared to uncoated ones [12,18]. In addition, Wafa et al. showed that the success rate of using DAIR as well as two-stage revision to treat infected silver-coated megaprosthesis was significantly higher than when used to treat infected uncoated implants [12]. Zajonz et al. reported that reinfection rate after healed reinfection in the silver group was slightly better than the non-silver group (40 vs. 57%) [19].

Hardes et al. showed that silver levels in the serum were detected up to 24 months post implantation of sliver-coated prostheses [20]. Also, there were no reports of toxicity or adverse local tissue reaction in patients treated with silver-coated implants. Despite these promising results, there are only a handful of studies that reported on outcomes after using these coated implants.

DAIR

The DAIR procedure is one of the treatment approaches described for PJI of endoprostheses in cancer patients. However, treatment outcomes after DAIR are highly variable and unpredictable in an oncology setting. Success rates vary between 39-70% [1,9,12,17,21]. Reported factors that are associated with better outcomes after DAIR include superficial early infection, short duration of symptoms, well-fixed implants and well-characterized microbiology demonstrating a highly susceptible pathogen [13,15,22]. Unfortunately, the studies that reported on DAIR outcomes have a highly variable period of clinical follow-up (34 months–10 years).

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TABLE 1. Evidence table

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Bus 2017 [21]	Retrospective cohort 2008–2014	N = 47 LUMIC reconstruction for pelvic tumor	* 69% DAIR * 31% implant removal	3.9 years	* 28% had infection. * 69% were successfully treated with DAIR (2). * 31% needed implant removal. Two had amputation, 1 rotationplasty and 1 LUMIC prosthesis. * More blood loss was associated with a higher risk of infection; other factors were not associated.
Chambers 1962 [23]	Narrative review	X	X	X	* Article on the bactericidal effects of silver (1f).
Dhanoa 2015 [1]	Retrospective cohort 2007–2011	N = 105 Endoprosthetic reconstruction for tumor	* 54% DAIR * 46% 2-SR	32 months	* 12.4% infection at 0-63 months. * Higher risk after additional procedures (13x), comorbidity, proximal tibia endoprostheses, pelvic endoprostheses and preoperative hospitalization >48 hour. Lower risk with distal femoral prostheses. * 80% of infections had operations >2.5h, compared to 16.3% in non-infections. * 38% *Staph aureus*, 31% CNS, 23% Klebsiella pneumoniae, 23% Pseudomonas aeruginosa. 38.5% had polymicrobial infection (1d). * 80% of 2-SR were successful; 1 patient had antibiotic suppression. * 43% of DAIR were successful; 2 patients had antibiotics; 2 patients had amputation (2).
Donati 2016 [18]	Retrospective case-control 2005–2016	N = 68 Megaprosthesis reconstruction for proximal femur tumors	X	47 months (12-114 months)	* Overall infection rate 11.8% at mean 25 months: silver 7.9%, control 16.7% (1f). * In late infection, explanted megaprostheses had important degradation of the coating surface (1f). * No differences in functional scores between silver and control (1f). * No local or general signs of toxicity (1f).
Felden 2015 [24]	Prospective cohort 1995–2011	N = 45 Pelvic irradiation before cemented THA	X	51 months (17-137 months)	* Patient survival was 71% at 2y, 52% at 5y and 41% at 10y. * The cumulative probability of revision was 2.2% at 1y, 2.2% at 2y, 8.1% at 5y and 20.2% at 10y. * 6% underwent revision for infection, 1 treated with 2-SR, 2 treated with 1-SR (all successful).
Flint 2007 [2]	Prospective cohort 1989–2004	N = 15 Infection after uncemented Kotz prostheses for bone sarcoma	2-SR	42 months (3-150 months)	* Prosthetic infection occurred at mean 28 months (1-132 months). * 75% CNS, 33% *Staph aureus*, 8% Pseudomonas aeruginosa, 8% E. coli, 8% Streptococcus viridans (1d). * 73% had second-stage revision: 27% had amputation, 73% with infection control after second-stage. * 60% success with retention of diaphyseal stems; 40% success with removal of anchorage pieces. * No relation between success and anatomical location or infecting organism (1d). * 66% of failures had previous radiation (1c). * In case of infection within 6 months 86% of 2-SR was successful, after 6 months only 25%.

TABLE 1. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Funovics 2011 [7]	Retrospective cohort 1982–2008	N = 166 Endoprosthetic reconstruction for tumor	* 83% 1-SR * 8% muscle flap * 8% deceased	47 months (0-365 months)	* Survival rate without infection was 95.9% at 1y, 89.2% at 5y, 89.2% at 10y and 77.8% at 20y. * 7.2% had infection at mean 39 months (0-167 months). * 30% CNS, 30% Staph epidermidis. Polymicrobial infection in 30.8% (1d). * Higher rate of infection in primary tumors, cemented prostheses, pelvic reconstruction, additional operations or radiotherapy (1c). * 63% infection control by 1-SR, 13% additional 1-SR, 25% additional 2-SR.
Gitelis 2008 [25]	No full text	X	X	X	X
Grimer 2002 [3]	Prospective cohort 1989–1998	N = 34 Infection after endoprostheses for sarcoma	2-SR	6-116 months	* Obvious causes of infection included lengthening or rebushing procedures, infected ingrown toenail, chest infection, infected burn blister, infected Hickman catheter and neutropenic septicaemia. * 53% CNS, 32% *Staph aureus*, 6% streptococci, 3% Enterobacter and 3% Corynebacterium (1d). * 70% had infection control after 2-SR. 6% needed amputation within 6 months. 6% needed additional 2-SR (1 successful, 1 not). 18% had late infections with various treatments. * Overall success rate for controlling infection was 94% at 6 months, 91% at 1 year, 74% at 5 years and 65% at 10 years. * Reinfection occurred in all 3 patients with previous radiotherapy (1c). * Functional outcome after successful infection control was mean 77% MSTS (47-100%).
Hardes 2006 [8]	Retrospective cohort 1992–2003	N = 30 Infection after MUTARS tumor endoprostheses for sarcoma	* 3.3% antibiotics * 10% 1-SR * 80% 2-SR	32 months (3-128 months)	* Infection occurred at mean time 16 months (1-70 months). * 62% CNS, 21% *Staph aureus*, 14% Enterococcus species. 21% had polymicrobial infections (1d). * 1-SR was successful in 33%, 2-SR in 63% * 33% of 2-SR failures needed amputation, 33% rotationarthroplasty, 11% arthrodesis, 22% retained the spacer (1 died after 4 months, 1 had satisfactory function). * 8.3% needed a change of spacer (1f). * The most important risk factor for failed limb salvage was poor soft tissue. * Chemotherapy, time of occurrence of infection, virulence and type of infection had no influence (1b). * A mean of 2.6 revision operations per patients, mean duration of hospital stay 68 days.
Hardes 2007 [20]	Prospective cohort 2002–2004	N = 20 Silver-coated MUTARS tumor endoprostheses for metastasis	X	19 months (2-32 months)	* No patients had signs of local or systemic argyrosis (1f). * The mean serum silver concentration was 0.37 ppb preoperatively, 2.80 ppb 2 week postoperatively. Between 2 and 24 months silver concentration varied from 1.93 – 12.98 ppb (1f). * 10 patients showed decreased glomerular filtration rates (1f). * The silver-coating was intact in all patients. Histologic examination showed no signs of chronic inflammation, granulomas or necrotic tissue (1f).

TABLE 1. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Hardes 2010 [26]	Prospective case-control 2005–2009	N = 51 (74 control) Silver-coated replacement for bone or soft-tissue tumors	Various	19 months (3-63 months)	* 5.9% with silver had infections compared to 17.6% with titanium prostheses, at mean 11 months (1f). * Patients with infection had longer operating time (305 vs. 228 minutes). * 38.5% with titanium prostheses had amputation or rotationplasty for infection, 0% in silver group (1f). * In the silver group 2 were treated with antibiotics alone, 1 had minor revision (one-stage without removal of the stem), all were successful (1f).
Henderson 2011 [27]	Retrospective cohort 1974–2008	N = 2,174 Limb preservation with metallic endoprostheses for tumor	X	X	* 24.5% were considered failures, of which 12% had soft tissue problems, 19% aseptic loosening, 17% fracture, 17% tumor progression, 34% infection. * Infection occurred more often in hinged prostheses than in polyaxial protheses ($p < 0.05$). * Failure incidence decreased over time. The mean time to failure was 47 months. * Literature review of 4359 patients with 29% failures.
Hollinger 1996 [28]	No full text	X	X	X	X
Hsu 1999 [29]	Prospective cohort 1975–1986	N = 38 Limb salvage for tumors needing revision surgery	* 50% revision * 32% amputation * 10% arthrodesis * 8% miscellaneous	51 months	* Indications for reoperation were aseptic loosening (34%), instability (13%), infection (13%), tumor recurrence (13%), fracture (11%) and miscellaneous (16%). * 16% died after revision at a mean of 40 months after revision. * After revision functional results were excellent (12.5%), good (81.3%) or fair (6.25%). * 63% had radiolucent zones immediately after revision. 25% of these developed progressive changes that had an effect on limb function. * Patients with revision had higher survival rates and longer disease-free intervals than patients with amputation ($p < 0.01$). * Overall 18.4% had complications: 5.3% aseptic loosening, 5.3% infection, 2.6% non-union, 2.6% local recurrence and 2.6% instability.
Jacobs 1995 [30]	Retrospective cohort 1983–1991	N = 9 Uncemented THA with previous pelvic irradiation	X	37 months (17-78 months)	* 4/9 radiographic and clinical migrations, 2/4 had revision, of which 1 needed Girdlestone after revision (1c).

TABLE 1. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Jeys 2003 [31]	Retrospective cohort 1966–2001	N = 1,261 Endoprostetic replacement	Amputation	5.2 years	* Overall patient survival was 60% at 5 years, 54% at 10 years and 40% at 20 years. * Overall limb survival without amputation was excellent with 91% at 20 years. * Overall risk of amputation was 8.9% of which the reasons were local recurrence (63%), infection (34%), mechanical failure (2%) and persistent pain (1%). * Risk of amputation after infection was 19% compared to 36% for local recurrence. * Time to amputation was a mean of 32 months for infection.
Jeys 2005 [4]	Retrospective cohort 1966–2001	N = 1,240 Prosthetic replacement for bone tumor	* 43% 2-SR * 32% amputation * 24% 1-SR * 2% Girdlestone	5.8 years (0.3-34 years)	* 11% had infection from 1996-2001 3.7%, 14% from 1966-1996. * 88% presented within 2 years after the last surgical procedure. * 48% had Staphylococcus epidermidis, 26% had polymicrobial infection (1d). * Polymicrobial infections did not reduce the rate of successful treatment of infection (1d). * Success rates: amputation 98%, 2-SR 72%, Girdlestone 50%, 1-SR 42%.
Jeys 2007 [32]	Retrospective cohort 1966–2001	N = 412 Endoprosthetic reconstruction for osteosarcoma	X	6.7 years (0-20 years)	* 10% had deep infection at mean time 4.6 months. * 52% had Staph epidermidis, 29% Staph aureus (1d). * There was better survival in patients infected with Staphylococcus (10y survival 92%, mixed organisms 79%, no infection 62.2%, Streptococcus 50%) (1d). * There was no evidence that patients with infections had more effective chemotherapy (1b). * There were more infections after radiotherapy (p=0.02) (1c).
Jeys 2007 [16]	Retrospective cohort 1966–2001	N = 1,254 63 radiotherapy Endoprosthetic replacement for bone tumor	X	5.8 years (0.3-33 years)	* Mean postoperative MSTS function score was lower after radiotherapy (64% vs. 81.3%) (1c). * Risk of infection without radiotherapy 9.8%, preoperative radiotherapy 20.7%, postoperative radiotherapy 35.3% (1c). * Risk of amputation without radiotherapy 7.8%, preoparative radiotherapy 17.2%, postoperative radiotherapy 14.7% (1c). * 10y survival was worse after radiotherapy (29%) than without radiotherapy (58%) (1c).
Jeys 2009 [33]	No full text (chapter book)	X	X	X	X
Kaminsky 2017 [34]	No full text	X	X	X	X

TABLE 1. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Kim 2007 [35]	Prospective cohort 1997–2003	N = 51 Uncemented THA with irradiation of the pelvis for adenocarcinoma of the prostate	X	4.8 years (2-7.5 years)	* 47% had radiation induced osteonecrosis of the femoral head (1c). * 6% had wound discharge, which healed without surgical treatment (1c). * 2% had deep infection, which required subsequent resection arthroplasty (successful) (1c).
Lansdown 2010 [36]	Narrative review	X	X	X	* Paper about the mechanisms of absorption and metabolism of silver in the human body, presumed mechanisms of argyria and the elimination of silver-protein complexes in the bile and urine (1f). * Argyria and argyrosis are the principle effects associated with heavy deposition of insoluble silver precipitates in the dermis and cornea/conjunctiva. Argyria is not associated with pathological damage (1f).
Lee 2002 [5]	Retrospective cohort 1985–1998	N = 145 18 infection Tumor prosthesis for bone and soft tissue tumors	* 78% DAIR * 11% 2-SR * 11% 1-SR	44 months (5-136 months)	* 12.4% had infection at mean 8 months (0.5-54 months). * 39% was successfully treated with DAIR or revision; 17% needed arthrodesis and 11% amputation (2). * 100% of 2-SR were successful, 0% of 1-SR were successful. * 33% with uncontrolled infection by DAIR and refused prosthesis removal had suppressive antibiotics. * The knee joint seemed to show poor outcome, but this was not statistically meaningful. * Infection control was poor in cases of cementless fixation ($p < 0.01$). * Chemotherapy gave a higher risk of infection (18.7% vs. 5.6%) (1b). * Soft tissue defects (sinus, pus discharge, wound dehiscence) correlated with poor prognosis ($p < 0.05$).
Li 2011 [22]	Retrospective cohort 1993–2008	N = 53 Endoprosthetic reconstruction for sarcoma	DAIR	10 years	* 1.9% had early infection, successfully treated with DAIR (2). * 5.7% had late infections, all treated with DAIR. One was successful, 2 needed revision (successful) (2). * 7.5% had wound complications requiring repeat surgery (debridement and closure) (2).
Manoso 2006 [17]	Retrospective cohort 1990–2001	N = 11 Infected knee reconstruction after limb-salvage surgery for cancer treated with staged protocol	Staged reconstruction protocol	X	* 82% had chronic infection, with a sinus tract in 45% at mean time 6 months (1-210 months). * 45% had failed DAIRs (2). * 55% had Staph aureus, 27% had Staph epidermidis. In 55%, a single organism caused the infection (1d). * 82% were immunocompromised with the administration of chemotherapy at the time of infection (1b). * All limbs were spared without amputation or flap loss. Overall cure rate was 91%. * Early complications were 2 peroneal palsies and 1 venous flap congestion requiring wound revision. * The mean functional outcome was 23/30 and mean knee range of motion 98 degrees.

TABLE 1. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Massin 1995 [37]	Excluded	X	X	X	X
Mavrogenis 2015 [13]	Retrospective cohort 1983–2010	N = 1,161 Megaprosthesis reconstruction after limb salvage surgery for sarcoma	* 83% 2-SR * 12% 1-SR * 5% amputation	Mean 9 years (3-20 years)	* 8.6% had infection at mean time 3.7y. * Most common isolates were Staph epidermidis (47%), *Staph aureus* (19%) and pseudomonas (6%) (1d). * Overall survival rate of megaprostheses was 88% at 10y and 84% at 20y. * Survival was higher for cementless reconstruction, not different for type of megaprosthesis, site of reconstruction or adjuvant therapy (1b).
Mavrogenis 2011 [15]	Narrative review	X	X	X	* DAIR may be effective in early infections, with short duration of symptoms, well-fixed implants and ideally with well-characterized microbiology demonstrating a highly susceptible pathogen (2). * Success in 2-SR 72-91%, 1-SR 42% and amputation 98-100%. * 2-SR is recommended for persistent infections, antibiotic-resistant pathogens or failed 1-SR. In well-fixed cementless modular prostheses anchorage stems can be retained. * Disadvantages of 2-SR are long hospitalization, increased bone loss, disuse osteoporosis, difficult revision operations and shortening of the affected limb. * Reimplantation should be delayed after completion of chemotherapy (1b). * An antibiotic-loaded cement spacer is essential in 2-SR; added antibiotics should be heatstable (1e). * Most surgeons administer systemic antibiotics 6 weeks, with reimplantation after > 2 months (1a).
McDonald 1990 [11]	Retrospective cohort 1970–1986	N = 304 271 malignant 33 benign Prosthesis or non-biological spacer in limb salvage surgery for primary bone tumors	X	2 years	* 11.8% had infection, 22% of these patients needed amputation. * Adjuvant and neo-adjuvant chemotherapy gave a higher risk of complications (32.8% and 55.4% vs. 25.2%). Reconstruction with uncemented prostheses had fewest complications (1b).
Mittermayer 2002 [38]	Excluded	X	X	X	X
Morii 2010 [14]	Retrospective cohort 2000–2008	N = 82 Endoprosthetic reconstruction for knee tumors	X	52 months (9-105 months)	* 17% had infection at mean time 10.9 months. * 50% had *Staph aureus*, 30% Staph epidermidis and 10% Pseudomonas (1d). * Age, sex, tumor origin, co-morbidities, operating time, blood loss, chemotherapy, clean air operating room, extracapsular resection, prosthesis type, number of postoperative antibiotics, posterior muscle flap were not risk factors for infection (1b). * Skin necrosis and surface infection were risk factors for infection.

TABLE 1. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Morii 2013 [6]	Retrospective cohort 1995–2009	N = 388 Endoprosthetic reconstruction for knee tumors	* 45% debridement * 14% 2-SR * 10% amputation * 9% 1-SR * 7% soft tissue flap	66 months (5-213 months)	* 14.6% had infection at mean time 13 months. * 47% Staph aureus and 17.5% Staph epidermidis (1d). * Infections were controlled in 84.2% the others had an accepted fistula or suppressive antibiotics. * Patients with diabetes, bone metastasis, lack of gastrocnemius flap coverage and pus required more surgical interventions for infection control. * The most successful therapy was 2-SR (80% success). Therapies with prosthesis removal were more successful than other therapies.
Peel 2014 [9]	Retrospective cohort 1996–2010	N = 121 Tumor endoprostheses surgery	* 53% DAIR * 24% 2-SR * 12% 1-SR * 6% resection * 6% amputation	34 months (17-80 months)	* 14% had infection at median time 18 months * Parenteral antibiotics median 9 days (0-58), 82% received oral combination antibiotic therapy with rifampicin (365 days) (1a). * Success rates: DAIR 75%, 1-SR 100%, 2-SR 50%, resection 0%, amputation 100% (2). * The majority of treatment failures occurred in patients with multi-resistant organisms (1d).
Pilge 2012 [39]	No full text	X	X	X	X
Racano 2013 [10]	Systematic review 1990–2011	N = 4,838 in 48 level IV studies	X	X	* Pooled infection rate was 10% (0-25%). * Most common organisms were Staph aureus and Staph epidermidis (1d). * There is considerable variation in antibiotic regimens. 0-24 hour antibiotic prophylaxis had 13% infection, >24 hour prophylaxis had 8% infection ($p < 0.05$) (1a).
Renard 2000 [40]	Prospective cohort 1975–1995	N = 77 Limb saving surgery (50) or ablative surgery (25) for sarcoma	X	97 months (28-271 months)	* 6% had deep infection, leading to amputation in 2/3 cases. * 4% had superficial infection successfully treated with DAIR and gentamicin beads (2).
Sherman 2008 [41]	Excluded	X	X	X	X
Shin 1999 [42]	Retrospective cohort 1970–1990	N = 52 41 malignant 11 benign Limb salvage surgery for musculoskeletal tumor	* 67% revision * 21% amputation * 8% arthrodesis * 2% fibular graft * 2% ORIF	12 years (37-296 months)	* 11.5% had infection. * Functional rating was 63%. Pain 69%, function 53%, emotional acceptance 72%, support 60%, walking ability 62%, gait 54%, hand positioning 66%, manual dexterity 94% and lifting ability 63%. * After revision 33% needed reoperation for complications: 58% aseptic loosening, 25% infection, 17% prosthetic failure and 8% patellar dislocation. * Survival after reoperation was 79% (5y) and 65% (10y).

TABLE 1. Evidence table (*Cont.*)

Author and Year	Study Type	Patients	Procedures	Follow-up	Major Outcomes
Sim 2007 [43]	Retrospective cohort 1996 – 2005	N = 50 Endoprosthetic reconstruction for knee tumors (GRMS)	3 washouts	24.5 months (2-124 months)	* Patients with metastatic disease or pathological fractures did not have higher complication rates. * 12% had deep infection for which patients received multiple washouts and long-term antibiotics (2). * 1/6 had revision; 1/6 had amputation (2).
Wafa 2015 [12]	Prospective case-control 2006–2011	N = 170 Reconstruction with silver-enhanced endoprostheses for several indications	X	12 months	* 11.8% infection in silver group, 22.4% in control group (1f). * Higher incidence of Pseudomonas in the silver group (1d/1f). * 70% of infected prosthesis was successfully treated with DAIR, 31.6% in the control group (1f/2). * 15.3% required implant removal, amputation or antibiotic suppression, 3.5% in the silver group (1f). * 18.8% with adjuvant chemotherapy developed infection (1b). * 15% had relapse infection after 2-SR in the silver group, 42.9% in the control group (1f).
Wirganowicz 1999 [44]	Prospective cohort 1980–1995	N = 64 Failed endoprostheses for neoplastic disease	* 75% revision * 25% amputation	2 years	* 13% failed because of an infection. * 50% of infected prostheses had revision with the same prosthesis, 25% with a different prosthesis and 25% underwent amputation. * Patients receiving revision endoprostheses were not at increased risk for a subsequent revision or amputation compared to primary endoprostheses reconstruction.
Zajonz 2016 [19]	Retrospective cohort 1994–2014 Excluded	N = 34 Modular endoprostheses of the lower extremity for infection	X	72 months (6-267 months)	* Reinfection rate after healed reinfection in silver group was 40%, in the non-silver group 57% (1f).
Zajonz 2017 [45]	Retrospective cohort 1994–2011	N = 101 45 tumor Modular endoprostheses of the lower extremity	* 62% 2-SR * 11% resection * 11% arthrodesis * 8% DAIR * 8% amputation	27 months (5-179 months)	* 17.7% had infection (3 early infections, 16 late infections), reinfection rate 37%. * 36.6% CNS, 26.3% Staph epidermidis, 15.8% *Staph aureus* (1d). * Patients with infection had same age and sex, but higher BMI. * Prosthesis for tumors had fewer infections than other indications (8.9% vs. 21.7%).

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QUESTION 2: What is the best reconstruction technique for an infected allograft?

RECOMMENDATION: The best reconstruction technique for an infected allograft is resection of the infected allograft and reconstruction (preferable two-stage) with an endoprosthesis.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 0%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Use of allograft in the reconstruction of a massive bone defect created by resection of a tumor is frequently successful. However, as with all tumor reconstruction methods, it is also plagued with complications, infection being one of them. A number of observational studies have been published on the subject. The largest case series by Mankin et al. described 121 allograft infections in 945 patients accounting to an infection rate of 12.8% [1]. The study did not, however, address management of the infected allograft. A more recent systematic review by Aponte et al. [2] reviewed the available literature and infection rates reported in previous studies [3–7]. The infection rate of allograft used after tumor resection ranged from 8.5% to 13.3%. The infection rate in their own series was 9% with 60 infections in 673 patients who received massive allografts after oncological resections. Only 18% (11/60) of the patients in that cohort were successfully treated by debridement and antibiotics with salvage of the original allograft. Of the 41 patients who underwent two-stage revision, 24 were revised with allograft and 17 with endoprostheses. Reinfection occurred in 14 patients of which 12 were in the allograft group and 2 were in the endoprostheses group. This demonstrated a lesser rate of reinfection when revision to endoprostheses was done as opposed to revision to another allograft.

Our search did not find any reports of revision to a vascularized fibular autograft or treatment with bone transport. Although these are both biological methods of reconstruction and their efficacy in the treatment of bone defects created by trauma and infection as well as for primary reconstruction following tumor resection is well established [8,9].

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QUESTION 3: What is the best surgical treatment for management of a chronically infected oncologic endoprosthesis? Does this change if the patient is receiving or has received recent chemotherapy and/or irradiation?

RECOMMENDATION: We recommend a two-stage revision in the management of a chronically infected oncologic endoprosthesis; however, we acknowledge that support for a one-stage exchange is increasing. There is no study to suggest that this recommendation should change if the patient is receiving or has received recent chemotherapy and/or irradiation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 0%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Although the use of an endoprosthesis in the treatment of musculoskeletal tumors has many advantages, infection of the endoprosthetic device is a significant complication. In addition to eradicating the infection, the goal in treating these infections is to salvage the limb and avoid amputation. There are numerous interventions used in the management of an endoprosthetic infection, including irrigation and debridement, one-stage revision, two-stage revision and amputation as a last resort.

Jeys et al. demonstrated that two-stage revision was able to eradicate infection in 42 of 58 patients (72%), compared to a 47% (15 of 32) success rate with one-stage revision and a 6% (4 of 68) success rate with local surgical debridement with or without antibiotics [1]. Morii et al. reinforce the idea that two-stage revisions have better outcomes compared to both a one-stage exchange and irrigation and debridement [2]. Finally, investigators in Malaysia reported an 80% success rate with two-stage revision compared to a 42.8% success rate with surgical debridement without a change of the implant [3].

In addition to greater success rates, two-stage revision has demonstrated greater functional outcomes. Grimer et al. assessed the functional outcome of patients with a successful two-stage revision using the Musculoskeletal Tumor Society functional evaluation score. The scores ranged from 47% to 100% with a mean of 77% [4]. One study reviewed one-stage exchange which demonstrated a 77.8% success rate and suggested that one-stage revision of infected megaprostheses without exchange of anchorage components is a sensible and useful choice for patients with antibiotic-sensitive microorganisms [5].

Given these results, we have concluded that two-stage revision is currently more supported by literature as a surgical treatment for the management of a chronically infected oncologic endoprosthesis. However, due to the presence of some conflicting data, the strength of this recommendation is limited, and we do believe that one-stage exchange with or without exchange of anchorage components may represent a feasible option.

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PART V

TRAUMA

Prevention

1.1. PREVENTION: HOST FACTORS

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QUESTION 1: What is the relationship between smoking and infection in fracture procedures? Is smoking history or only current smoking important? Does nicotine cessation at time of fracture reduce complication rates?

RECOMMENDATION: Smoking seems to increase the risk of infection in fracture procedures. The importance of smoking history versus current smoking status is unknown. It is also unknown if nicotine cessation (smoking) at time of fracture treatment reduces complication rates.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Smoking has been seen to have a negative effect in physiological and biological pathways. It interferes with the coagulation cascade (smokers clot faster), it impairs vascular function, and also interferes with the immune system (alters neutrophil function, migration and action) [1–5]. Even after smoking cessation, neutrophil phagocytic function continues to be impaired. Monocyte and macrophage correct function are key to prevent infection caused by *S. aureus* or *E. coli*, two of the most common infection-causing pathogens [3,4]. Smoking also affects the proliferative and remodelling phases of healing [6] by compromising epidermal regeneration and neovascularization and by causing decrease in perfusion and oxygenation [7,8].

The relationship between smoking and complications after fracture procedures has been widely studied [9,10]. Available literature suggests that smoking increases the overall incidence of complications including the risk for non-union and surgical site infection (SSI) [9–14]. Although the latter has not been consistent throughout studies, many authors continue to investigate this relationship.

Some available studies have not found smoking to be a definitive risk factor for infection [9–14]. One case control study that compared 140 smoking and 133 non-smoking patients with open tibia fractures suggested that infection might be multifactorial and not related to a single event [11]. A different prospective cohort study evaluating patients with limb-threatening open tibia fractures showed that current smokers were twice as likely to develop an infection compared to non-smokers (odds ratio (OR) 2.2; $p = 0.05$) [12]. That same study observed that previous smokers, compared to non-smokers, did not show any difference in terms of infection risk (OR 1.00; $p = 0.99$). Court-Brown et al. evaluated 178 patients who underwent fixation after calcaneal fractures [15]. They evaluated factors associated with infection including time to surgery, level of experience of the attending, smoking and type of wound closure. None of these were shown to be associated with infection. A randomized control trial allocated 105 smokers with a fracture requiring surgical treatment to a quit-smoking group ($n = 50$) or a non-quit-smoking group ($n = 55$) [16]. They found that the odds for presenting with a complication (superficial infection being the most common) was 2.51 times higher in the group that continued smoking compared to those who quit smoking, although this did not reach statistical significance. With similar findings, a recent systematic review found that there was no increased risk in smokers either for superficial or deep infection ($p = 0.13$ and $p = 0.33$, respectively) [14]. In terms of deep infection, retrospective studies have evaluated intramedullary nailing of tibia shaft fractures [17], open reduction and internal fixation (ORIF) of pilon fractures [18] and ORIF of acetabular fractures [19]. These concluded that there is no statistical significance related to smoking and increased infection rates. The most recent published study also showed that there was no statistically significant increased risk of infection in relation to smoking ($p = 0.45$) [20].

There is also evidence suggesting that smoking clearly increases the risk of infection in fracture procedures. Nasell et al. [13] evaluated 906 patients with ankle fractures that developed deep wound infections. They reported that these were more likely to be smokers than non-smokers (4.9% versus 0.8%; $p < 0.001$). They concluded that smoking was a risk factor associated with both deep and superficial wound infections (OR 6.0 and 1.7, respectively). Morris et al. [21] published a retrospective cohort study that included 302 bicondylar tibia plateau fractures treated with ORIF. Smoking was identified as the most important risk factor for deep infection (OR 2.40; $p = 0.02$). That same year Ovaska et al. [22] published a prospective cohort study that included 1,923 ankle surgeries with 131 deep surgical site infections. Smoking was shown to be statistically significant relative to infection in both the univariate (OR 4.0; $p = 0.004$) and multivariate analyses (OR 4.1; $p = 0.017$).

Two additional studies evaluated smoking-related complications in lower limb fractures. One consisted of a retrospective cohort study that included 519 patients with distal tibia fractures [23]. Smoking was associated with overall complications including infection (OR 3.40; $p = 0.039$). The second evaluated 30-day postoperative complications after ankle fracture fixation in a prospective cohort study [24]. They concluded that among the predictors for major local complications (deep wound infection and reoperation) peripheral vascular disease, open wound, contaminated wound classification and smoking (OR 2.85; $p = 0.0031$) were the strongest. Evidence from the last two years reveal smoking as an independent risk factor for

wound infection, as presented in a retrospective study managing 1,320 elbow fractures [25] and a case-control study from 318 calcaneal fractures [26]. In the first study, only smoking was found to have an association with infection after multivariate analysis (adjusted OR = 2.2; p = 0.023); the second study revealed that higher body mass index, delayed operation and active smoking (OR 19.497, p < .001) represented an increased risk for wound infection after ORIF.

Despite the conflicting evidence found in the literature, smoking seems to have a negative effect on overall complications and health and could potentially lead to an increased risk of infection. It is well-established that smoking has a detrimental effect on tissue healing and cellular pathways. Nonetheless, the current literature lacks the high-level evidence to state a direct relationship between these two factors. The recommendation provided here is inconclusive.

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QUESTION 2: What is the role of nutritional supplementation (NS) in avoiding infection in acute fracture cases?

RECOMMENDATION: (1) Evidence does not support the role of NS for avoiding infections in well-nourished individuals. (2) However, the literature has stated that in patients with a nutritional deficiency or catabolic state restoring nutritional parameters might reduce the risk of infection.

LEVEL OF EVIDENCE: (1) Limited, (2) Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Evidence in the available literature demonstrates that malnutrition is a significant clinical and public health problem. Several clinical trials present NS as a global effort in medicine, with applications in different specialties to improve the general condition of patients

with malnutrition or metabolic stress secondary to trauma or infection and to modulate the inflammatory response and potentially mitigate negative outcomes. Although there are controversial results, in spite of several studies with evidence level I on both supporting and refuting this initiative [1–7]. The literature has shown certain indications for prescription of NS in surgery, most recently defined by the European Society for Clinical Nutrition and Metabolism (ESPEN) guideline in 2017 [2]. There are two published meta-analyses concerning the effect of perioperative oral NS on elderly patients after hip surgery. The first combined 10 randomized control trials (RCTs) involving 986 elderly patients, which showed that oral NS had a positive effect on the serum total protein ($p < 0.00001$) and led to a significantly decreased number of complications ($p = 0.0005$). Furthermore, data from the infection subgroups showed significant decreases in wound infection (odds ratio (OR) = 0.17; 95% confidence interval (CI): 0.04, 0.79; $p = 0.02$), respiratory infection (OR = 0.26; 95% CI: 0.07, 0.94; $p = 0.04$), and urinary tract infection (OR = 0.22; 95% CI: 0.05, 0.90; $p = 0.03$) [6]. The second pooled the results from 11 RCTs (multinutrient, oral, nasogastric and intravenous supplementation), with an NS group of 370 elderly people controlled with a group of 357 elderly, non-NS patients. This study demonstrated a reduction in complication rates (e.g., pressure sores, chest infection) at 1-12 months in the NS group (123/370 versus 157/ 367; relative risk (RR) 0.71; 95% CI 0.59 to 0.86) [7], but not on rates of surgical site infection (SSI). However, NS use in an elderly population with acute fractures remains controversial and the prescription is reserved for underfed or malnourished patients in an attempt to reduce complications during hospitalization [2,6]. According to the World Health Organization (WHO) and ESPEN, malnutrition is considered when a patient has a 10-15% weight loss within six months, 5% in three months and/or has a Body Mass Index (BMI) under 18.5 kg/m^2. There are hematologic parameters evaluated throughout the literature, such as a serum albumin/globulin ratio below 1.5 (normal range), albumin below 3.0 g/dl, lymphocyte count below 1,500 cells/mm^3 and a lymphocyte//monocyte ratio below five versus one that allows selective screening of suspected malnutrition [3,5,8–10]. This is a special topic of interest in patients with factures, due to the fact that approximately 50% of patients with orthopaedic infections had some degree of malnutrition and immunosuppression regardless of age [3].

Evidence favoring NS has revealed that supplementation containing protein could produce beneficial effects by reducing the risk of infection in patients with fractures and nutrition deficiencies, regardless of age [2,4,5,11]. In a 2012 clinical trial, Myint et al. describe significant differences in BMI comparing the supplementation arm versus a control group [4]. Also, NS also prevents weight loss during a prolonged hospital stay, improving the general state of the muscles and muscular strength, which could reduce hospitalization periods and thus lead to shorter exposure to nosocomial microorganisms [7,12]. Long et al. reported that patients with poor nutritional status and with infections lose a higher amount of protein during postoperative states through urine [13]. Furthermore, an altered nutritional status reflects a depleted physiological state that affects humoral and/or cellular immunity, limiting an effective response to infection [3]. These findings might explain why early enteral administration of NS reduces the risk of septic shock with an active infectious process [12]. NS also seems to prevent long periods of delirium, which in turn is associated with an increased mortality rate [14].

Despite the previous evidence, there is also available literature against the use of NS [7,12,15]. For instance, NS administration near the time of surgical intervention does not seem to have an important effect, as it cannot effectively change the traditional nutritional markers such as albumin or transferrin [8]. However, in a 2012 clinical trial, Gunnarsson et al. reported evidence of the utility of monitoring the insulin-like growth-factor 1 to evaluate the response of nutritional support in the short term [9].

Some studies report that NS should be used with caution, considering metabolic phenomena such as refeeding syndrome, a condition associated with quick NS in patients with severe malnutrition. In this case, a sudden increase in insulin stimulates hypophosphatemia and produces a decrease in the extracellular adenosine triphosphate (ATP) and two to three diphosphoglycerate on erythrocytes producing arrhythmia, respiratory failure and hematologic alterations. Prevention, monitoring and adequate dosage are key to the success of preventing such complication [16–18]. Standard nutritional supplements containing arginine, omega-3 fatty acid, glutamine and other components (immunonutrition) have level I evidence supporting its use in avoiding infection after colorectal resection [1].

Another meta-analysis (eight RCTs and two observational studies) showed that multiple nutrient-enhanced formulas demonstrate a benefit in reducing the risk of SSI compared to standard NS (very low-quality evidence) [19]. The population studied included adult patients undergoing major surgical procedures (mainly cancer and cardiac patients). Orthopaedic surgical procedures, however, were not included in this meta-analysis.

In conclusion, these results suggest that NS can have positive effects on avoiding wound infection and other infectious complications (respiratory infection, urinary tract infection) only in elderly patients after hip surgery. There are several limitations in the current literature with respect to recommending NS in acute fractures for every patient. It would be necessary to conduct further research to investigate the role of immunonutrition in orthopaedics, especially with respect to fractures.

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QUESTION 3: Do preoperative pneumonia/urinary tract infections (UTIs)/trophic ulcers increase periprosthetic joint infection/surgical site infection (PJI/SSI) risk in femoral neck fracture patients treated by partial/total hip arthroplasty (THA)?

RECOMMENDATION: There is a paucity of literature examining whether pneumonia/UTI/trophic ulcers increase SSI/PJI risk for patients with femoral neck fractured treated by hemi- or THA.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 91%, Disagree: 0%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

Infection after femoral neck fracture treated with hemiarthroplasty/THA is an uncommon but devastating problem. The current literature cites a 1.7 to 7.3% risk of SSI after hemiarthroplasty for femoral neck fracture [1]. Commonly-cited risk factors for PJI/SSI after hemiarthroplasty for femoral neck fracture include higher Body Mass Index (BMI), prolonged surgery time, preoperative elevation in C-reactive protein (CRP) levels, surgeon experience level, reoperation and hematoma formation [2,3].

For patients undergoing primary total joint arthroplasty, pneumonia, UTIs and skin ulceration were shown to be predisposing factors for developing PJI [4–8]. However, there remains a lack of publications that specifically examine the risk of PJI/SSI related to the preoperative presence of pneumonia, UTI or skin ulceration in patients with femoral neck fracture treated with hemiarthroplasty or THA. One small prospective study demonstrated that UTI preoperatively was a significant risk factor for infection (odds ratio = 10; p = 0.04) [9]. A systematic review of the literature indicated that two or more urinary tract catheterizations during hospitalization was identified as a risk factor for SSI [1]. After a thorough investigation, we could not find any existing evidence of an association between preoperative pneumonia or trophic ulcers with the development of PJI/SSI after hemiarthroplasty or total hip replacement for femoral neck fractures.

In summary, there is scant or no evidence to suggest that preoperative pneumonia/UTI/trophic ulcers result in an increase in PJI/SSI risk in femoral neck fracture patients treated by partial/THA. The little evidence that is available is low quality and suggests that preoperative urinary tract infection increases the odds of PJI after hemiarthroplasty. Higher quality and larger scale studies are necessary in this subset population to make valid conclusions on this possible relationship.

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QUESTION 4: Are there microorganism-specific risk factors for acute infection in trauma patients (i.e., does being a nasal carrier of methicillin-resistant *Staphylococcus aureus* (*S. aureus*), or MRSA, increase the risk for MRSA infection after trauma?)

RECOMMENDATION: The current evidence of an increased risk of infection is based on several risk factors, including MRSA colonization, presence of external fixator, anatomical location of surgery and severe open fractures. In these situations, alterations in antibiotic prophylaxis could be considered.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

MRSA colonization in the nares, axilla and other body sites has been associated with higher risk for MRSA surgical site infection (SSI) (cardiac and arthroplasties) [1]. Nasal topical decolonization, along with systemic antibiotic prophylaxis, has been shown to reduce the risk of MRSA prosthetic joint infections (PJIs) [2]. In a meta-analysis published by Schweizer et al. a bundle intervention consisting of nasal decolonization and glycopeptide prophylaxis showed a significant protective effect against MRSA PJI and cardiac surgical infection when all patients underwent decolonization (0.40, 0.29 to 0.55) and when only *S. aureus* carriers underwent decolonization (0.36, 0.22 to 0.57). Because only three randomized clinical trials (RCTs) assessed the risk associated with total joint arthroplasty, they also included seven studies assessing nasal decolonization for general orthopaedic surgeries. Most of decolonization regimens used mupirocin ointment into the anterior nares. In addition, seven studies assessed the bundle applied only for patients colonized with MRSA and found a significant protective effect against SSIs with gram-positive bacteria (0.41, 0.30 to 0.56) [3]. Therefore, there is a strong recommendation to perform nasal decolonization for those patients known to be at high risk for MRSA PJI.

However, nasal colonization with MRSA as an independent risk factor for MRSA infection after orthopaedic trauma and fractures has yet to be investigated. Taormina el al. prospectively assessed whether trauma patients with fracture nonunions who are colonized with nasal *S. aureus* (MRSA or methicillin-susceptible *S. aureus* (MSSA)) would be at greater risk of complications following surgeries, and if it would predict positive operative cultures. The study failed to demonstrate an association between MRSA or MSSA-colonized patients being treated for fracture nonunion of long bones with postoperative infectious complications. There was no significant difference in operative culture positivity or speciation between colonized or non-colonized patients [4]. On the other hand, in recent a non-randomized, 7-year prospective study in Japan, Nakamura et al. examined the role of preoperative nasal swabbing for *S. aureus* among patients who underwent several types of orthopaedic surgeries. One hundred and forty patients were MRSA nasal carriers (carriage rate 3.4%), even though only a minority of them (40) underwent osteosynthesis for fracture stabilization [5]. Nasal carriage of *S. aureus* or MRSA developed significantly more SSIs compared to non-carriers, suggesting that it may be a risk factor for SSI in orthopaedic surgery. Additionally, Croft at al. prospectively screened for MRSA colonization in 355 patients admitted to a trauma intensive care unit, of which 36 (10.1%) were colonized. Significantly higher rates of MRSA infection were diagnosed in the MRSA colonized group (33.3%) compared to those who were not (6.6%) ($p < 0.001$). Death rates were also higher among the colonized group compared to non-colonized patients, (22.2 vs. 5.% [$p < 0.001$]). Therefore, they recommended MRSA screening protocols at trauma units to identify these at-risk patients [6].

The current evidence that MRSA colonization predicts acute infection in trauma patients is scarce, but it suggests that assessment and decolonization may be beneficial in reducing fracture-fixation infection rates. Nixon et al. screened 1,122 trauma patients, of whom 3.8% were MRSA carriers, and after implementation of anti-MRSA policies the incidence of MRSA infection dropped by 56% [7]. The same group, in a retrospective study, identified 3.2% (79/2,473) MRSA carriage at admission in an acute trauma unit, and these patients were significantly more likely to develop MRSA SSI (7 of 79 patients, 8.8%) compared with 54/2,394 (2.3%) of MRSA-negative patients ($p < 0.001$). This difference was confirmed on multivariate analysis, in which the odds ratio for developing MRSA SSI among MRSA carriers was 2.5 ($p = 0.015$) [8].

Conversely, Kan et al. analyzed 66 patients with femoral neck fractures and rates of MRSA colonization and found no correlation between MRSA colonization and higher rates of postoperative infection. Nevertheless, this study presented several important limitations including the postoperative infection evaluation limited to the first immediate postoperative week and short follow-up evaluation no longer than four months [9].

Older patients with femoral neck fractures seem to be particularly prone to be colonized by MRSA. A large French retrospective multicenter cohort study identified an SSI rate of 5.6% in patients who had surgery for a proximal femur fracture, of which one-third involved MRSA. All infected patients received first-generation or second-generation cephalosporin for prophylaxis, whereas those who received antibiotics effective against MRSA (i.e., vancomycin or gentamicin) for prophylaxis had no MRSA SSI [10]. Similarly, a prospective cohort study assessed the MRSA colonization rates among patients with proximal femur fracture in a German trauma unit. Their conclusion and recommendation is to systematically search for MRSA colonization in patients presenting with known risk factors by swabbing them in the emergency room [11].

The role of MRSA carriage eradication among trauma patients admitted to the intensive care unit (ICU) as an independent measure to prevent MRSA infection was assessed in a large multi-center, patient-based RCT recently published by Maxwell et al. Those with positive nasal swabs were randomized to either daily chlorhexidine gluconate (CHG) baths and mupirocin (MUP) ointment to the nares or soap and water baths and placebo ointment (S + P) for five days. Upon admission, 13.3% (90/678) of patients were MRSA carriers, and clinical MRSA infection was significantly more often diagnosed in MRSA colonized patients (21.1%) than those who were not (5.4%, $p < 0.001$). Although underpowered to draw definitive conclusions regarding the role of MRSA decolonization with CHG + MUP to

reduce MRSA infection rates, due to the smaller number of recruited patients per treatment arm, the five-day treatment period resulted in only a trend towards the reduction of colonization, 13 (59.1%) vs. 9 (90%) for CHG + MUP vs. S + P (p = 0.114). There was no difference in the proportion of MRSA infections between CHG + MUP (seven [31.8%]) vs. S + P (six [60%], p = 0.244). CHG + MUP was ineffective in eradicating MRSA from the anterior nares, but may reduce the incidence of infection [12].

A pilot RCT evaluated SSI among patients with open fractures that received prophylaxis during 24 hours with cefazolin compared with vancomycin and cefazolin, depending upon their *S. aureus* colonization status. MSSA and MRSA carriers were 20% and 3%, respectively. Although underpowered with a sample size too small for a clinical efficacy analysis, no significant difference in the rates of SSI was observed between the treatment arms. A significantly higher rate of MRSA SSIs was observed among MRSA carriers compared with noncarriers (33% vs. 1%, respectively, p = 0.003) [13]. Other factors that raise the risk of MRSA infection include the use of external fixation and a prolonged time to intramedullary nailing of long bone fractures [14].

Torbert's retrospective study identified *S. aureus* and gram-negative rods (GNRs) as most commonly seen in deep postoperative infections. GNRs were seen more frequently in the pelvis acetabulum and proximal femur injuries even in closed fractures. Resistance to GNRs was lower than *S. aureus,* and the infection rates for combined surgical approaches were twice that of a single approach for acetabular or pelvic surgery [15].

Severity of open fracture plays a role in the choice of antibiotics. There was no statistically significant difference in infection rates between the group treated with ciprofloxacin and that treated with cefamandole/gentamicin for Types I and II open fracture wounds. A high failure rate for the ciprofloxacin only treated Type III open fracture group, with patients being 5.33 times more likely to become infected than those in the combination therapy group [16].

The anatomic location of surgery should be considered when administering preoperative antibiotics. Corynebacterium genera are frequently associated with implants when surgical incisions were made near the perineum [17]. *Cutibacterium acnes* is bacterial species that is often seen in the axilla and coverage for these organisms should be considered when operating near this anatomical location [18].

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QUESTION 5: Is periprosthetic fracture a risk for the development of a periprosthetic joint infection (PJI)?

RECOMMENDATION: Infection rates from level III and IV evidence studies suggest an increased surgical site infection in patients who undergo re-operation for treatment of periprosthetic fracture of the femur after total hip and knee arthroplasty. There is limited literature available on periprosthetic acetabular and tibial fractures. Further study investigating the outcomes for treatment of periprosthetic fracture is recommended.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Periprosthetic fracture about a hip or knee replacement can be a devastating complication. Almost all studies involving periprosthetic fractures are limited to small, retrospective case series and many of the studies focus on one type of treatment for one type of fracture. Additionally, most of these studies focus on the return to function and union of the fracture as primary endpoints. As a result, there is limited data on the risk of surgical site infection in the presence of a periprosthetic fracture.

Periprosthetic fractures about the acetabular component of a total hip replacement are uncommon and typically involve high-energy injuries. Treatment is based on the fracture pattern and stability of the implant. Protected weightbearing or revision surgery, often with supplemental fixation, are utilized for treatment. A retrospective review of 11 patients did not discuss infection as a complication [1].

Periprosthetic fractures about the femoral component of a total hip replacement are most commonly reported in the literature. These fractures can be treated either nonoperatively or surgically, based on the fracture pattern and stability of the implant. Plate fixation, revision hip arthroplasty or combination treatment are the most common methods of surgical treatment. A study from the Swedish joint replacement registry identified 1,049 periprosthetic femur fractures treated surgically over a 21-year period. Over this period, 245 patients underwent re-operation, the most common reasons for failure being loosening, re-fracture and non-union. There was an infection rate of 2.3% (24 cases), and infection was more common in the plate fixation group than the revision hip arthroplasty group [2].

A study from the Mayo Clinic demonstrated 5 (4.2%) deep periprosthetic infections after femoral component revision of 118 Vancouver Type B periprosthetic fractures [3]. Similarly, a systematic review of 22 studies totaling 510 Vancouver Type B2 and B3 fractures demonstrated 13 (2.5%) surgical site infections [4]. In cases of extremely poor bone stock, a retrospective review demonstrated a 19% infection rate in 19 proximal femoral replacements [5].

Periprosthetic fractures about the distal femur after total knee replacement can be treated nonoperatively or surgically based on the fracture pattern and stability of the implant. Fractures can be treated with intra-medullary nail fixation, plate fixation or revision knee arthroplasty. A systematic review of 415 fractures from 29 case series demonstrated an infection rate of 3% [6].

Periprosthetic fractures about the tibia after total knee replacement are rare (0.4 to 1.7%) and can often be treated nonoperatively [7,8]. Surgical treatment with plate fixation, intramedullary nail fixation or revision arthroplasty is uncommon, and the current literature is limited to small retrospective case series.

While randomization would be difficult due to limited previous experience with these complicated cases, future study should involve prospective, multi-centered investigations involving larger numbers of patients to gain a better understanding of the natural history and outcomes of patients who undergo treatment for periprosthetic fractures.

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QUESTION 6: Are there predictors of the need for allogeneic blood transfusion (ABT) in patients undergoing arthroplasty for acute hip fractures?

RECOMMENDATION: Preoperative predictors for the need for ABT include (1) anemia and (2) dementia and hypoalbuminemia. (3) Anticoagulation or anti-platelet medications do not predict the need for ABT. There is conflicting data with regard to the need for ABT when comparing hemiarthroplasty (HA) to total hip arthroplasty (THA).

LEVEL OF EVIDENCE: (1) Strong, (2) Limited, (3) Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Preoperative anemia is a known risk factor for ABT in patients undergoing hip and knee arthroplasty [1,2]. A retrospective study of 1,484 patients with hip fractures from 2007 to 2010 identified the risk factors for ABT as older age, lower hemoglobin on admission, female gender, type of surgical implant used (cephalomedullary nail and dynamic hip screw more than HA) and a shorter time from admission to surgery. The study is limited by transfusion thresholds, which may artificially increase the rate of ABT [3]. In hip fracture patients, regardless of fixation or fracture type, hypoalbuminemia [4] and dementia [5] are associated with an increased need for ABT.

Patients on chronic anticoagulation therapy are thought to be at risk for perioperative complications associated with bleeding. A level III retrospective study matched 62 patients with proximal femur fractures on warfarin with 62 patients not on anticoagulation therapy treated with an intramedullary nail, HA or THA. There was no significant difference in the rates of ABT in patients with international normalized ratio (INR) < 1.5 or with subgroup analysis of patients with an INR > 1.5 (range 1.5 to 3.1) [6]. There are three retrospective studies evaluating the preoperative use of clopidogrel in hip fracture patients with matched control patients comparing blood transfusion rates that report no significant increase in ABT [7–9].

A systematic review and meta-analysis of studies comparing surgical approaches and four studies comparing surgical approach for HA showed no difference in ABT rates between anterior, lateral and posterior approaches [10–13].

Perioperatively, medications such as hemocoagulase agkistrodon and tranexamic acid are administered to decrease blood loss. Multiple studies in the setting of femoral neck fracture have demonstrated a lower rate of ABT using these medications, but there remains a concern for increased risk of venous thromboembolism [14–17].

Much debate has centered on the treatment for displaced femoral neck fractures. Three prospective randomized controlled trials demonstrate no significant difference in the rate of ABT between cemented versus cementless femoral fixation in HA [18–20]. Multiple studies have reviewed differences between HA and THA for femoral neck fracture. Findings include longer operating times and increased blood loss in THA, but these studies can be difficult to interpret as patients undergoing THA are often younger and healthier [21,22]. Studies have demonstrated no difference in the rate of ABT [22,23], and increased rate of ABT in THA [21,24].

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1.2. PREVENTION: RISK MITIGATION

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QUESTION 1: Is there a role for bacterial decolonization (i.e., of methicillin-resistant *Staphylococcus aureus* (*S. aureus*), or MRSA, in nares) in trauma cases?

RECOMMENDATION: It is unknown if bacterial decolonization in trauma patients reduces surgical site infection (SSI).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

S. aureus colonization has been described since the early 1930s, and is linked to postoperative SSI in different surgical specialties, including orthopaedics. *S. aureus* resides in the nares, throat and skin surfaces in up to 30% of the population [1]. Establishing an association between bacterial carrier status and SSI in the setting of orthopaedic trauma has been challenging. The reported rate of MRSA carriers ranges from 1.8% up to 30% of hip and femur fracture patients [2–11], whereas the reported rates of MRSA-related SSI in those carrier populations ranges from 8.8% to 14.2% [6,12]. Furthermore, MRSA carriers displayed a higher incidence of other nosocomial infections and one-year mortality [4].

Although several published studies do support a connection between preoperative carrier status (for MRSA) with postoperative SSI development [13], it is uncertain whether it is due to the carrier status alone or due to other patient and disease factors [14]. One study refuted the need for widespread MRSA screening and eradication [15]. On the other hand, most literature has advocated addressing high-risk populations [6,9,16–18] for carrier status with prophylactic antibiotics against MRSA rather than decolonization preoperatively. Two main reasons have been postulated. First, one study found that in 86% of trauma cases in the setting of emergency fracture management, the results of MRSA screening would not be available before the surgical procedure commences [2]. Second, successful decolonization process will delay surgical procedures, which may not be ideal especially in hip fractures and open fractures.

With regard to decolonization, MRSA-related SSI was significantly reduced after decolonization protocol (without any reference to carrier status) from 2.3% to 0.33% [19]. However, one study demonstrated that MRSA screening and treatment policy reduced infection rates from 1.57% to 0.69% [5]. Furthermore, decolonization has been found to decrease total numbers of wound infection rather than wound infections caused by *S. aureus* [20].

For orthopaedic trauma cases, no prospective study of bacterial decolonization exists. The introduction of MRSA screening policies was evaluated in two retrospective studies including trauma patients [5,21]. Mupirocin was used for MRSA-positive patients, and both studies showed a significant reduction of postoperative MRSA infections. In a recent study on patients with lower extremity fractures, the addition of a povidone-iodine nasal swab in addition to a chlorhexidine-gluconate bath was evaluated [22]. Compared to two years before the start of the povidone-iodine intervention, the rate of SSI declined significantly.

Literature supporting decolonization in orthopaedic trauma patients only consists of low to moderate quality level 3 and 4 studies [19,20]. Literature not supporting decolonization consisted of one moderate quality level 1 study [23] and one low quality level 4 study [7]. As a result, a recommendation could not be made in favor of or against bacterial decolonization. Most importantly, screening should not delay surgical intervention in these patients, and these should be individually evaluated in a case by case scenario.

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QUESTION 2: What are the ideal strategies to prevent secondary and nosocomial contamination of open fracture wounds which are left open?

RECOMMENDATION: Data support local antibiotics and early wound closure to reduce contamination of open facture wounds.

NOTE: The recommendation above was changed from the original version so the rationale below does not completely align with this recommendation. Please see Section 3:2, Question 2 for rationale for early wound closure. The rationale below regarding negative pressure wound therapy (NPWT) applies to Section 3:2, Question 4.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

METHODS

Randomized controlled trials, nonrandomized trials, prospective and retrospective observational studies were eligible for inclusion. We searched Medline, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to March 2018 for published studies without language restriction. Our search strategy, including keywords and MeSH headings, are provided in the Appendix. Eligible studies met the following criteria: (1) all patients included in the study had an open fracture, (2) infection was an outcome variable and (3) there was a comparison between patients treated with a secondary infection prevention strategy and a control group or a comparison between two or more secondary infection prevention strategies.

RATIONALE

Some high-grade open fractures are left open and return to the operating room for one or more repeat debridement surgeries. Traditionally the wound was packed with a gauze dressing, which was changed between surgeries. There is interest in using different strategies to decrease surgical site infection (SSI), which is often thought to be caused by nosocomial pathogens. The two main current treatment strategies are the use of the NPWT (wound VAC) or antibiotic bead pouches.

A systematic review of the literature reveals four randomized trials with conflicting results investigating the practice of NPWT over simple gauze dressings between surgical debridement, and there are no randomized trials examining the efficacy of antibiotic bead pouches.

Until recently, the literature investigating the use of NPWT tended to show a reduction in infection rates with its use. However, this conclusion was contradicted recently by the WOLFF trial [1] which is a well-powered (n = 460) prospective trial on open fractures requiring multiple debridements. Patients were randomized to either standard dressings or NPWT. No effect on SSI was shown (7% in negative pressure vs. 8% in standard dressing, p = 0.64) [2].

Prior to the publication of the WOLFF trial, the literature had consistently favored NPWT but in smaller or lower-quality studies as summarized in a recently-published systematic review of the literature [3]. Three of the papers included in the review assessed the effect of NPWT on reducing SSI in open fractures [4–6]. There have been two additional randomized trials published more recently [7,8] and we identified two other retrospective studies on this topic [2,9]. Two of the three prior randomized trials demonstrated reduction in infection with NPWT (28% vs. 5%, p = 0.02, n = 62 [4] and 11% vs. 5%, p < 0.05, n = 93 [7]) and the third (n = 90) had a very low event rate and revealed no difference [8]. Three more retrospective studies showed similar results with relatively large reductions in infection rates with NPWT (55% vs. 19%, p = 0.04 [8], 21% vs. 8%, p = 0.01 [3], 33% vs. 10%, p = 0.03 [2]), and a fourth identified no difference despite a potential selection bias against NPWT due to higher-risk cases in that group [8].

Despite the widespread use of this technique in North America, there are few studies investigating the use of local antibiotic beads. These are composed of polymethal methacrylate (PMMA) cement mixed with antibiotics placed into the wound in a "bead pouch" that seals off the wound between debridement surgeries. One small pilot randomized trial investigated IV antibiotics versus antibiotic beads without intravenous (IV) antibiotics and found no difference in infection rates [10]. Three similar retrospective studies by one group [11–13] should probably be considered as one study, as all the

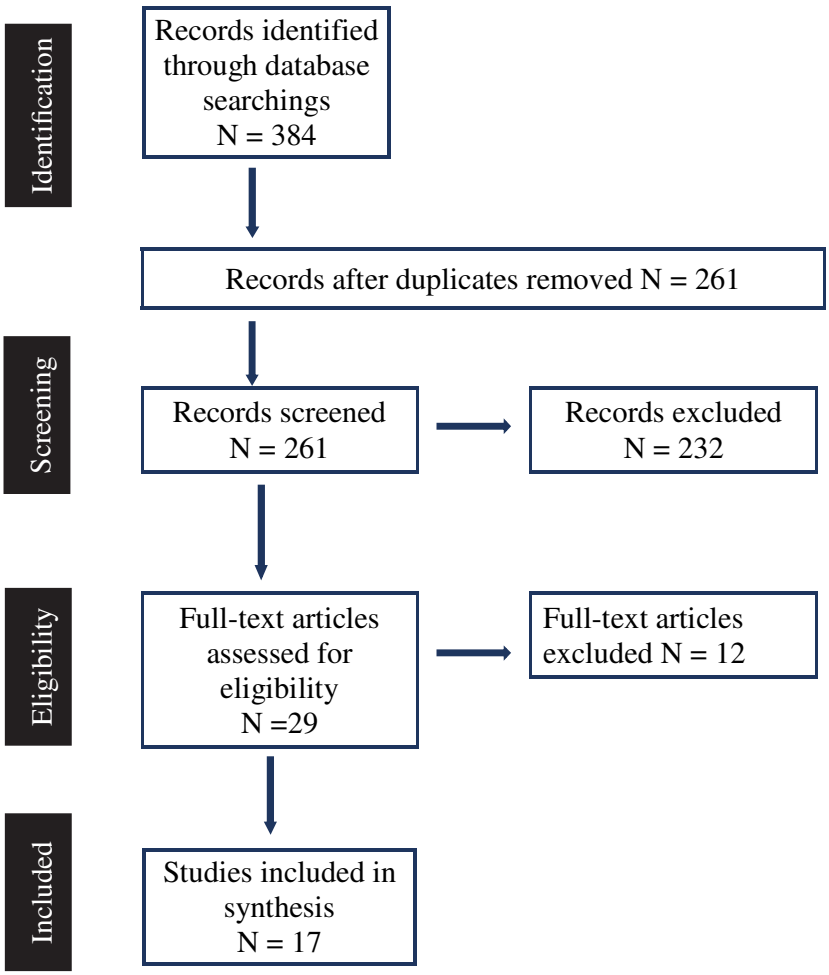

FIGURE 1. Flow diagram of study selection.

patients in one study appear to be included in the later study. This work demonstrated a significant reduction of infection rates (12% vs. 3.7%, p = 0.001) [12].

This said, one of the most important preventive measures seems to be the actual use of local antibiotics. A recent meta-analysis by Morgenstern et al., not included in this research strategy, suggests a risk reduction in infection of 11.9% if additional local antibiotics are given prophylactically for open limb fractures. Most studies in this review used PMMA beads as local carrier for the antibiotics [14]. Furthermore, support for the use of topical antibiotics in open wounds is from recent animal studies in rats [15–17] and goats [18] by a single research group using contaminated open fracture models.

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APPENDIX – SEARCH STRATEGY (NO PUBLICATION DATE LIMIT)

Ovid Medline – 120 references retrieved on 03/22/2018
((open adj3 fracture*).ab,ti. OR "Fractures, Open".sh.) **AND**
((infection* or sepsis OR contamination).ab,ti. or Infection/ or "Wound Infection".sh. or "Cross Infection".sh. or "Sepsis".sh.) **AND**
((beads OR "bead chains" OR "vacuum assisted closure" OR VAC OR "vacuum sealing" OR gel).ab,ti. OR "Negative-Pressure Wound Therapy".sh.)

Embase – 215 references retrieved on 03/22/2018
((open NEXT/3 fracture*):ab,ti OR 'open fracture'/de) **AND**
(infection*:ab,ti OR sepsis:ab,ti OR contamination:ab,ti OR 'infection'/exp OR 'wound infection'/de OR 'cross infection'/de OR 'hospital infection'/de OR 'sepsis'/exp) **AND**
(beads:ab,ti OR "bead chains":ab,ti OR "vacuum assisted closure":de,ab,ti OR VAC:ab,ti OR "vacuum sealing":ab,ti OR gel:ab,ti)
CINAHL – 35 references retrieved on 03/22/2018
((open W3 fracture*) OR MH Fractures, Open) **AND**
(infection* OR sepsis OR contamination) **AND**
(beads OR bead chains OR vacuum assisted closure OR VAC OR vacuum sealing OR MH "Negative Pressure Wound Therapy")

CENTRAL – 14 references retrieved on 03/22/2018 – in Title, Abstract, Keywords
(open NEAR/3 fracture*) **AND**
(infection* OR sepsis OR contamination) **AND**
(beads OR "bead chains" OR "vacuum assisted closure" OR VAC OR "vacuum sealing" OR gel)

Authors: Mitch Harris, Sofiene Kallel, Abhiram R. Bhashyam, Andre Shaffer

QUESTION 3: Is there a difference in the risk of periprosthetic joint infection (PJI) with use of internal versus external fixation for treatment of periprosthetic fractures?

RECOMMENDATION: Unknown. There is limited evidence comparing the risk of PJI with use of internal versus external fixation to treat periprosthetic fracture. The potential for pin tract infection, particularly with inadvertently placed intra-articular pins, make internal fixation the preferable treatment option in most cases.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 5%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The majority of studies that have explored this question describe periprosthetic femur fractures after total knee arthroplasty (TKA). Periprosthetic femur fractures following TKA are an uncommon complication (0.3 to 2.5% incidence rate per year), but are occurring more frequently given the higher rate of primary TKA and increased activity of the elderly patients who are at the highest risk [1–3]. Treatment options currently include nonoperative management (protected weightbearing, bracing, casting), open reduction internal fixation (ORIF), or, rarely, external fixation [1,4]. Given the success of ORIF, there are few reports on the use of external fixation [1,2,4]. In addition, external fixation has historically been avoided given the belief that external fixation pins near a total joint increases the risk for superficial and deep infection [2].

Within this specific clinical setting, there is limited knowledge given the lack of large series of periprosthetic femur fractures treated with either internal or external fixation. The only reports of external fixation for these fractures are case reports. Based on the current literature, there is no difference in the rate of deep infection following internal fixation (rate = 4%) versus external fixation (rate = 7%, p = 0.8). This analysis is severely limited by the small sample size, so it is difficult to make any definitive statement regarding the differential risk for PJI after internal or external fixation of periprosthetic fractures.

ORIF is preferred given its high rates of union and low rates of infection (~ 3%) [1,2,4]. For patients who are too ill or are contra-indicated for ORIF, treatment options include nonoperative management or external fixation. While the infection rate for nonoperative treatment is predictably low (0 to 1%), 31% of patients had complications related to malunion or nonunion [2,3]. Given this poor outcome, some have turned to external fixation [3,5–9].

A recent systematic review found that the rate of deep infection/PJI following ORIF was 4.1% (10 out of 245 reported patients). Among all published reports using external fixation, the rate of superficial pin site infection was 28.6% (4 out of 14 reported patients) and the rate of deep infection/PJI was 7.1% (1 out of 14 reported patients) [3,5–9]. The rate of PJI between internal versus external fixation was not statistically significant (p = 0.8 by chi-square test). Based on this data, the risk of PJI is not statistically significantly different following internal or external fixation of periprosthetic femur fractures, but this analysis is severely limited by small sample size.

There are only two case series that report on use of external fixation to treat periprosthetic fractures. Assayag et al. successfully treated two periprosthetic tibia fractures using a circular external fixation frame without superficial or deep infection [10]. Interestingly, Sakai et al. successfully treated an infected periprosthetic total hip arthroplasty femoral fracture with Ilizarov external fixation with resolution of the infection [11].

There has been no systematic study of this topic. Thus, it is therefore challenging to make a definitive statement regarding any possible differential risk for PJI after internal or external fixation of periprosthetic fractures. Internal fixation appears to be the preferable treatment method with a trend toward lower risk of PJI, as well as the potential for improved alignment and function with better reduction and fixation.

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APPENDIX - SEARCH STRATEGY

Databases: OVID-Medline, Google Scholar, Scopus

1. "Periprosthetic Fractures"[MeSH] AND "Infection"[MeSH]) AND ("external fixation" or "internal fixation")
2. "infection" and "periprosthetic fracture" and ("internal fixation" vs. "external fixation")
3. "infection" and "periprosthetic hip fracture" and ("external fixation") - Nothing
4. "periprosthetic tibia fracture" and "external fixation" – 1
5. "periprosthetic femur fracture" and "external fixation" – 1

COMBINED ANALYSIS

Paper	N	Superficial Infection	Deep Infection
Beris	3	2	0
Figgie	1	1	1
Biswas	5	0	0
Merkel	3	0	0
Simon	1	1	0
Hurson	1	0	0
Summary	**14**	**4 (28.6%)**	**1 (7.1%)**

($p = 0.8$; chi square result compared to results following ORIF)

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QUESTION 4: Should definitive fixation of fracture in a polytrauma patient and open abdomen be delayed until the abdomen is closed?

RECOMMENDATION: Definitive fracture fixation in the presence of an open abdomen should not be delayed and could be performed safely if the patient is suitable to undergo surgery.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 95%, Disagree: 5%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Laparotomy is a well-established intervention in a polytrauma patient aimed to achieve rapid hemostasis and limit the contamination generated by intestinal, biliary or urinary leak [1–3]. However, abdomen closure cannot be carried out until edema has resolved to allow tension-free closure [1]. It is known that delayed abdominal closure after damage-control laparotomy reduces mortality, complications and length of stay. Nonetheless, definitive abdominal closure is not performed until the requirement for on-going resuscitation have ceased, no concerns regarding intestinal viability persist and no further surgical re-exploration is required [4]. Abdominal closure has been associated with fewer complications if performed within the the 4 to 7 days following laparotomy [4].

Early appropriate care of spine, pelvic ring, acetabulum and unstable femoral fractures in polytrauma patients decreases intensive care unit (ICU) length of stay from 9.4 to 4.5 days and total

hospital stay from 15.3 to 9.4 days [5]. However, definitive fracture fixation in patients with an open abdomen is often delayed due to the perceived increased risk of complications, specifically surgical site infection (SSI) [6].

One retrospective study has evaluated the safety of definitive fracture fixation in the presence of an open abdomen [6]. This study supports early definitive surgical management of spine, pelvic, acetabular and long bone fractures through minimally invasive techniques and standard open approaches. Time from injury to fixation surgery averaged 4.4 days when it was done in the presence of an open abdomen and 11.8 days when it was deferred until abdominal wall closure. The incidence of SSI that required surgical intervention was 3.1% in the first group and 30.6% in the second. No significant differences were found in terms of mortality, hospital length of stay or number of ventilator-dependent days.

Based on the limited available literature, there is no reason to delay definite fracture fixation in polytrauma patients with an open abdomen. Patients may benefit from early fracture fixation, not only from having reduced ICU and overall length of stay reduction, but infection risk reduction as well. We recommend that patients undergo definitive fracture fixation in the setting of an open abdomen if the patient is medically stable, does not have an active infection and is suitable to undergo surgery.

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Diagnosis

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QUESTION 1: Which open fracture classification system currently used (Gustilo-Anderson classification or the Orthopaedic Trauma Association's open fracture classification (OTA-OFC)) is preferred, based on interobserver reproducibility and predictiveness of outcomes?

RECOMMENDATION: OTA-OFC is preferred. Based on currently-available data, the OTA-OFC provides a more robust description of the injury with interobserver agreement that is comparable or superior to the Gustilo-Anderson classification. Additionally, the OTA-OFC, according to its subcategories, may predict outcomes such as the likelihood of early amputation and need for adjuvant treatments.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 95%, Disagree: 0%, Abstain: 5% (Unanimous, Strongest Consensus)

RATIONALE

The Gustilo-Anderson classification was introduced in 1976 for use in describing open fractures of the tibia [1,2]. Originally comprised of Types I through III, Type III was later subdivided into subtypes A through C to allow for the classification of "severe" fractures with greater specificity [2,3]. It has since been adopted for describing open fractures of all long bones and remains the most widely-used system for classifying open fractures [2].

The Gustilo-Anderson classification was found to have only moderate interobserver agreement when investigated by Horn et al. [4] and Brumbeck et al. [5], with an overall agreement of 66% and 60%, respectively. Clinically, the Gustilo-Anderson classification is well-established as a predictor of infection and amputation [1–3,6–8]. It provides a method of stratifying open fractures broadly into "mild" and "severe" categories.

The OTA-OFC was introduced in 2010 as a system for describing open fractures of all locations [9]. Rather than utilizing a single composite score, the OTA-OFC is comprised of five discrete components (skin, muscle, arterial, contamination and bone loss) each of which are independently rated mild, moderate or severe [9].

Studies suggest that inter-observer agreement throughout the OTA-OFC system is "moderate" to "good" overall [10,11], a statistic that is comparable or superior to that which has been reported for the Gustilo-Anderson classification [4,5,10]. This must be interpreted with caution, however, as the OTA-OFC is not aggregated and inter-observer agreement is not comparable among the five categories [10]. Studies assessing reliability have found that agreement is less robust within the muscle, bone loss, and contamination categories of OTA-OFC, suggesting that these categories may benefit from revision or clarification [10,11].

Initial studies in predictive utility of the OTA-OFC are promising. Agel et al. found different categories useful in predicting certain treatment modalities: the skin category for vacuum-assisted closure; bone loss category for antibiotic bead placement; skin and muscle categories for multiple debridements; and skin, contamination and arterial injury categories for early amputation [12]. Johnson et al. found it to be predictive of amputation and infection within 90 days [13]. Hao et al. found it to be predictive of amputation when the cumulative score was ≥ 10 [14].

While further studies validating the OTA-OFC are needed, the current literature suggests that it provides a method of describing open fractures with greater specificity compared to the Gustilo-Anderson classification with comparable inter-observer agreement.

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QUESTION 2: What diagnostic criteria must be fulfilled to diagnose surgical site infection (SSI) or fracture related infection (FRI) in orthopaedic trauma (including external fixators)?

RECOMMENDATION: Diagnostic criteria proposed by the International Consensus Group on FRI (published in 2017) should be used to diagnose infection in fracture cases. In cases, more than four weeks from fracture, histological confirmation of > 5 neutrophils per high power field is confirmatory of infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 85%, Disagree: 5%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

Unlike periprosthetic joint infections (PJI) which have clearly-defined diagnostic criteria [1], infection associated with orthopaedic trauma procedures does not. Orthopaedic trauma has a higher rate of SSIs compared to other surgical specialties, yet it lacks an infection definition agreement [2–4]. This is likely due to the great variety and complexity of skeletal trauma and variability of surgical procedures. According to the initial Centers for Disease Control and Prevention (CDC) definition of SSI in trauma, this could occur up to one year following surgery [5]. However, in their last revision, this time period has been reduced to 90 days [6]. This poses a challenge for diagnosis, since infections related to orthopaedic trauma are often subclinical and some only display pain without any other signs or symptoms [5,7]. Furthermore, the CDC guidelines distinguish between superficial incisional, deep incisional and organ/space infections. Bonnevialle et al. already stated that the term "superficial infection" is at best arbitrary [8], and poses particularly challenging problems in infection associated with orthopaedic trauma. Finally, in orthopaedic trauma research, these terms (e.g., superficial and deep) are often used inaccurately or inappropriately, which makes comparison of literature difficult [9]. In the current clinical literature, numerous terms other than SSI are used with respect to infections associated with orthopedic trauma procedures (e.g., posttraumatic osteomyelitis, osteitis). Often, no distinction is made between the terms osteitis and osteomyelitis. Overall, these terms seem not useful as the main issue is the presence of bacteria at the fracture site and around the implant, rather than the semantics of the pathogenesis of the infection [9].

Orthopaedic trauma surgeons realized that the definition for PJI, criteria for osteomyelitis and the CDC guidelines could not be easily extrapolated to fracture cases, and, therefore, a definition had to be developed. This was recently confirmed by an international survey for registered AOTrauma users. In this survey, surgeons were asked about the need for a working definition, and 90% of more than 2,000 surgeons who responded suggested that a definition solely focusing on infection in orthopaedic trauma (i.e., fractures) was required [10]. Therefore, a special effort was made, with the support of multipele orginazations, to develop (AO Foundation and European Bone and Joint Infection Society (EBJIS)) [9] and update (AO Foundation, Orthopaedic Trauma Association (OTA), EBJIS and PRO-Implant Foundation) [11] a consensus definition. The consensus group designated infection related to orthopaedic trauma (i.e., fractures) as FRIs and established a definition based on two different kinds of diagnostic criteria: confirmatory (infection definitely present if a confirmatory criterion is met) or suggestive (features associated with infection and requiring further investigation) criteria (Table 1).

Without question this consensus definition should be validated by prospective data collection in order to gather evidence of its use in clinical studies and to prove that it can become a valuable tool in comparative research.

TABLE 1. Criteria to define FRI

Confirmatory Criteria	Suggestive Criteria
1. Fistula, sinus or wound breakdown.	1. Clinical signs: pain increasing over time, local redness, local swelling, increased local temperature or fever.
2. Purulent drainage or presence of pus.	2. Radiological and nuclear imaging signs
3. Phenotypically indistinguishable pathogens identified by culture from at least two separate deep tissue/implant specimens.	3. Pathogenic organism identified by culture from a single deep tissue/implant specimen.
4. Presence of more than five polymorphonuclear neutrophil per high power field, confirmed by histopathological examination [12].	4. Elevated serum inflammatory markers: ESR, WBC, CRP
	5. Persistent or increasing wound drainage.
	6. New-onset of joint effusion in fracture patients.

FRI, fracture-related infection; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; WBC, white blood cell

External Fixation

The infection rates reported with the use of external fixators are higher than with osteosynthesis with an incidence of infection of up to 71% [13]. However, there is also no clarity in regards to the diagnosis of SSI in external fixation. There are two classification systems, Checketts-Otterburn and Sims, neither of which have been validated [13,14]. The most commonly used is the Checketts-Otterburn schema, which describes clinical signs such as redness, discharge, pain, edema, radiological changes in the screw-bone interface and compromise in several levels [15].

In conclusion, there is a scarcity of scientific evidence regarding diagnostic criteria to define SSIs in orthopaedic trauma. The CDC published guidelines for SSIs, which distinguish between superficial incisional, deep incisional and organ/space infections, seem not suitable to define/diagnose infection in orthopaedic trauma patients. The recently published, and thereafter updated, international consensus definition seems an adequate replacement. This definition introduces, instead of SSI, the term FRI. Furthermore, two levels of certainty around the diagnostic features are defined. Criteria can be confirmatory (infection definitely present if a confirmatory criterion is met) or suggestive. This definition should be validated by prospective data in the future.

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QUESTION 3: What diagnostic criteria define infected non-union of long bone?

RECOMMENDATION: The lack of scientific evidence precludes the development of diagnostic criteria that are solely based on sound evidence. The combination of the consensus definition of fracture-related infection (FRI) with a nonunion is a reasonable starting place, however definitions of nonunion vary and both the FRI definition and any proposed criteria for long bone nonunion will need scientific validation.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 86%, Disagree: 9%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Introduction

FRI is a feared musculoskeletal complication and one of the most challenging in trauma surgery. Currently, estimating the impact of FRI has been hampered by the lack of a clear definition [1,2]. Interestingly, this issue was previously raised in an Arbeitsgemeinschaft Osteosynthesefragen/Association for the Study of Internal Fixation (AO/ASIF) scientific supplement publication by Arens et al. in 1996, wherein the authors stated in a combined clinical and experimental study on FRI, "It is astonishing that in all papers in which infection is mentioned, the term 'infection' is not defined" [3]. In fact, this was confirmed by a recent systematic review, which showed that only a minority of randomized controlled trials (2%) in fracture cares use any kind of standardized definition of FRI [4]. The lack of a clear definition of FRI mirrors the situation for prosthetic joint infection (PJI) identified many years ago [1–5]. The situation for PJI [6] and diabetic foot infection, for example [7], has improved with consensus definitions emerging in recent years. Orthopaedic trauma surgeons realized that neither the definition for PJI nor the Centers for Disease Control and Prevention (CDC) guidelines could be easily extrapolated to fracture cases and that a definition for FRI had to be developed.

This was recently confirmed by an international survey for registered AOTrauma users. In this survey, surgeons were asked about the need for a working definition of FRI and 90% of more than

2,000 surgeons who responded suggested that a definition of FRI is required [8]. Therefore, a special effort was made, with the support of the AO Foundation, to develop such a consensus definition. The process that was followed was comparable to the one described by Cats-Baril et al. for the new definition on PJI [9]. Finally, in 2016, a consensus meeting concerning this topic was held with an international expert panel. This resulted in the current consensus definition for FRI, which was recently published [10]. This resulted in the current consensus definition for FRI, which was recently published and adopted by the AO Foundation and the European Bone and Joint Infection Society (EBJIS).

Classifications

There are multiple classifications described in the literature that subdivide FRI into discrete groupings, such as acute and chronic infections, or early, delayed and late-onset infections [2,11–13]. The authors of the recently-published consensus definition stated that there should only be a single definition for FRI based on specific diagnostic criteria. Two primary reasons were proposed for this decision. First, a subdivision would make such a definition unnecessarily complex and difficult to use in daily practice. Second, although the available classifications are time-related, these time windows are not based on scientific evidence. This supports the view that they are poorly-defined for FRI (e.g., time since injury, or time since onset of symptoms) and somewhat arbitrary. All these concerns pose serious problems from a definition point of view [4]. The authors did agree that acute and chronic infections are different entities that may require different treatment strategies, however it should not affect the way clinicians define FRI [10].

Diagnostic Criteria

Recent systematic reviews, of which two are currently under submission, have been performed to analyze the value of specific diagnostic criteria for FRI. Below, three systematic reviews on diagnostic criteria are summarized.

Clinical Criteria

Studies specifically focusing on clinical criteria to diagnose FRI are currently scarce and validation studies are nonexistent. In two systematic reviews, clinical criteria used to define FRI were described. In a study by Metsemakers et al., the aim was to identify definitions used in the literature to describe infectious complications after internal fixation of fractures [4]. A total of 100 randomized control trials (RCTs) were identified in the search. Clinical signs used to diagnose FRI in the included studies were: purulent drainage (16 studies), wound dehiscence/breakdown (5 studies), rubor (redness) (5 studies), calor (warmth) (4 studies), tumor (swelling) (4 studies), unspecified signs (4 studies) and fever (3 studies). Other parameters that were used to diagnose FRI were positive cultures (15 studies), treatment with oral antibiotics (6 studies), need for surgical debridement (5 studies), need for implant removal (4 studies), radiological signs (2 studies) and C-reactive protein (CRP) levels (1 study). Most authors included purulent drainage or discharge and positive cultures as parameters for the diagnosis of FRI [4].

In an ongoing systematic review by Bezstarosti et al., the authors are aiming to provide an overview of the available diagnostic criteria, classifications, treatment protocols and patient-related outcome measures for surgically treated FRIs between 1990 and 2017. Clinical signs used in the 93 included studies were: purulent drainage or discharge (34 studies), pain (14 studies), tumor (swelling) (9 studies), calor (warmth) (8 studies), wound dehiscence/breakdown (7 studies), rubor (redness) (7 studies), fever (5 studies) and unspecified signs (46 studies). It seems that swelling, pain and redness are often seen as signs of FRI, however, they are subject to interpretation and are difficult to measure. "Purulent drainage" and "wound dehiscence/breakdown" on the other hand, seem more appropriate as hard endpoints in the diagnosis of FRI.

Serum Inflammatory Markers

In an ongoing systematic review by van den Kieboom and Bosch et. al, the diagnostic value of the serum inflammatory markers CRP, leukocyte count (LC) and erythrocyte sedimentation rate (ESR) in suspected FRI were assessed. A total of 8,280 articles were identified, of which 6 [14–19] were included in this review. CRP, reported in 6 studies, appeared to be the most useful serum inflammatory marker with a sensitivity ranging between 60.0 and 100% and specificity between 34.3 and 85.7%, which is in line with current clinical practice [20]. LC was reported in five studies. Sensitivity ranged from 22.9 to 72.6% and specificity from 73.5 to 85.7%. Five studies investigated ESR; sensitivity and specificity ranged from 37.1 to 100% and 59.0 to 85.0% respectively. For the meta-analysis, four CRP studies, four LC studies and three ESR studies could be pooled. Meta-analysis of pooled results demonstrated only limited diagnostic value of the individual markers. Four studies analyzed the value of combining markers and reported an increased diagnostic accuracy. However, these results should be interpreted with caution as this is based on limited data from heterogeneous studies. Indeed, the results of all serum markers vary greatly between studies. Another issue identified when analyzing these studies was that different measuring devices, lab protocols and/or thresholds were used across studies. The authors, therefore, concluded that the analyzed serum inflammatory markers (CRP, LC and ESR) appear to be unsuitable to rule out or diagnose FRI. When these markers are used in a diagnostic flow chart, they should be interpreted with caution [10]. Future research protocols using continuous serum inflammatory marker values and standardized lab protocols are required to assess their combined value in the diagnosis of FRI.

Tissue and Sonication Fluid Sampling

In an ongoing systematic review, Onsea et al. analyzed the available evidence on sonication of fluid sampling and tissue tests for the diagnosis of FRI. Out of 2,624 studies, ten [14,21–29] fulfilled the predefined inclusion criteria. Five studies [21–25] focused on sonication fluid culture, two on polymerase chain reaction (PCR) [14,26] and two on histopathology [27,28]. One additional histopathology study [29] was found after screening of reference lists. The review demonstrated that there is evidence that sonication fluid culture may be a useful adjunct to conventional tissue culture, but there is no strong evidence that it is superior or can replace tissue culture. Regarding molecular techniques and histopathology, the evidence is even less clear. Overall, studies had variable gold standard definition criteria for comparison and poorly-reported culture methods. By updating the review, one additional paper [30] was found that is currently in press. In this study by Morgenstern et al., including unhealed FRI cases more than four weeks from the occurrence of the fracture, a bimodal cut-off for the presence of polymorphonuclears (PMNs) provided encouraging results in reducing the number of cases in which the diagnosis was uncertain [29]. During a recent second consensus meeting (i.e. AO Foundation, OTA, EBJIS and PRO-Implant Foundation) it was decided that this cut-off for the presence of PMN's was included as a confirmatory sign for FRI.

Finally, in the systematic review by Onsea et al., the authors concluded it is imperative that lab protocols become standardized and that uniform diagnostic criteria, as recently published in a consensus definition, are implemented.

Imaging Modalities

In a recent systematic review by Govaert et al. [31], the recent literature (from 2000 to 2016) on imaging techniques for the diagnosis of post-traumatic osteomyelitis was analyzed. The literature search yielded 3,358 original records, of which 10 articles [32–41] were included. This review included seven studies on different nuclear imaging techniques, two studies on magnetic resonance imaging (MRI), one study on computed tomography (CT) with no studies identified regarding plain X-ray. The sensitivity for white blood cell (WBC) count or anti-granulocyte antibody (AGA) scintigraphy ranged between 50 and 100%, specificity ranged between 40 and 97%. For fluorodeoxyglucose positron emission tomography (FDG-PET), sensitivity and specificity ranged between 83 and 100% and between 51 and 100%, respectively.

WBC scintigraphy combined with hybrid imaging technique of single photon emission computed tomography combined with CT (SPECT/CT) was assessed by two studies. A higher diagnostic accuracy was reported in both studies that used this combination. Three studies investigated the combination of FDG-PET with PET-CT, which provided a significant increase in diagnostic accuracy. However, the studies that looked into these combinations provided only limited information. The authors concluded that, compared to other imaging techniques, either WBC or AGA scintigraphy combined with SPECT/CT and FDG-PET combined with CT demonstrates the highest diagnostic accuracy for the diagnosis of post-traumatic osteomyelitis when compared to other imaging techniques. It should, however, be taken into account that these results are based on a small number of studies and that imaging techniques and patient populations were heterogeneous across studies.

By updating the systematic review, two more studies from the past two years could be found. A study by Govaert et al. [42], aimed to establish the accuracy of 192 WBC scintigraphies for diagnosing FRIs, and investigate whether the duration of the time interval between surgery and WBC scintigraphy influences its accuracy. The authors concluded that WBC scintigraphy had a diagnostic accuracy of 92% for the detection of FRI in the peripheral skeleton. The duration of the interval between surgery and the WBC scintigraphy did not influence its diagnostic accuracy. The second study, by van Vliet et al. [43], evaluated the efficacy and diagnostic accuracy of a semi-quantitative measure, maximum standard uptake value (SUVmax), for the interpretation of FDG-PET/CT in the differentiation between aseptic and septic delayed union of the lower extremity. A total of 30 patients were included: 13 patients with aseptic delayed unions and 17 patients with septic delayed unions. Mean SUVmax in aseptic delayed union patients was 3.23 (SD ± 1.21). Mean SUVmax in septic delayed union patients was 4.77 (SD ± 1.87). A cut-off SUVmax set at 4.0 showed a diagnostic accuracy of 70% to differentiate between aseptic and septic delayed union. The authors concluded that the application of SUVmax for the interpretation of FDG-PET/CT imaging seems to be a promising tool for the discrimination between aseptic and septic delayed union. However, as this is based on a small number of patients, they acknowledge that larger, prospective trials are necessary to make a further statement regarding the role of FDG-PET/CT in the diagnosis of FRI.

Due to the current lack of high-quality evidence on the value of imaging techniques, which is similar to the other diagnostic criteria discussed above, imaging techniques seem not suitable to rule out or diagnose FRI and can only be considered a suggestive sign [10]. This was also included in the recently updated (i.e. AO Foundation, OTA, EBJIS and PRO-Implant Foundation) international consensus definition of FRI.

The definition for non-union is currently not standardized, which makes it difficult to introduce diagnostic criteria for infected non-union. This said, overall there is little scientific evidence regarding the diagnostic criteria for FRI. With respect to serum inflammatory markers, tissue, sonication fluid sampling and imaging modalities, only a small number of studies are available. Validation studies on clinical parameters are nonexistent. This lack of scientific evidence precludes the development of diagnostic criteria that are solely based on sound evidence. Moreover, it seems that developing diagnostic criteria for *both* acute/early infections and chronic/late (e.g., infected nonunion) infections is arbitrary and complicates clinical decision-making. Finally, although the scientific evidence on diagnostic criteria to define FRI is scarce, the international Consensus definition of FRI that was recently updated seems an adequate start and offers clinicians the opportunity to standardize clinical reports and improve the quality of published literature. In our opinion, this definition should be validated by prospective data collection in the future.

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QUESTION 4: What differentiates acute from chronic osteomyelitis (OM)? Is it clinically important to distinguish one from the other?

RECOMMENDATION: Current literature is lacking consistent criteria for a distinct time point that differentiates the acute and chronic forms of infection. Differentiating between acute and chronic types may have practical implications on treatment plan and final prognosis.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 95%, Disagree: 5%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

To address this question an extensive search of the literature was conducted. Our search aim was to identify articles reporting on the diagnostic criteria for acute or chronic osteomyelitis. A clear definition of OM in terms of temporal evolution was considered mandatory. Furthermore, in order to investigate the potential practical significance of the temporal distinction of OM into acute or chronic types, we aimed to identify papers reporting on the outcome of antimicrobial therapy or combined treatment (antimicrobial plus surgical intervention) of acute osteomyelitis. Our exclusion criteria included case reports, expert opinions, experimental studies, infections associated with prosthetic implants, diabetic ulcers and non-orthopaedic bone infections (facial, cranium, ribs).

We searched the Medline, Embase, Ovid, Cochrane and Google Scholar databases using the PubMed search engine. Our search strategy included the following Medical Subject Headings (MeSH) terms and Boolean operators: ("osteomyelitis"[MeSH Terms] OR

"osteomyelitis"[All Fields]) OR "bone infection"[All Fields] OR "osseous infection"[All Fields] AND ("classification"[Subheading] OR "classification"[All Fields] OR "classification"[MeSH Terms]). This search process yielded 856 records. After rejection of duplicates and irrelevant articles by their title or abstract, there remained 45 papers for which full text was obtained. After careful screening against the eligibility criteria, there were ultimately eight eligible articles left.

A second search process was run in parallel, as follows: acute [All Fields] AND ("osteomyelitis"[MeSH Terms] OR "osteomyelitis"[All Fields]) AND "humans"[MeSH Terms]. It yielded 3,339 results. After removal of duplicates and rejection of irrelevant articles based on their title or abstract, there were 56 studies remaining, for which a full text was obtained. Eventually, after screening of these manuscripts against the eligibility criteria, another 11 eligible articles were obtained. In addition, another 4 articles were added from handsearch of the relevant bibliographies, leading to a total of 23 eligible articles (see Fig. 1).

OM is an inflammation of the bone and bone marrow caused commonly by pyogenic bacteria, and rather infrequently by mycobacteria or fungi [1,2]. It is classically classified by the duration of its clinical course as acute or chronic. Acute osteomyelitis represents the early stage of the evolutionary process of the disease, usually characterized by an intense clinical picture. Its diagnosis is based on a combination of clinical, laboratory and imaging findings, with a definitive diagnosis established by positive bacterial cultures of aspirate, bone or blood samples [3]. A longstanding infection which progresses to bone necrosis and sequestrum formation is termed chronic OM [1,2,4]. This condition is usually characterized by more subtle clinical findings, occasionally the presence of draining sinus tracts, or may progress intermittently [5]. While the clinical differentiation is marked by necrosis and sequestrum formation, defining a specific time threshold beyond which an acute infection could be considered chronic is difficult [1,2]. The current literature is lacking consistent criteria for a distinct time point that differentiates the acute and chronic forms of infection. Nevertheless, this distinction is of only limited value in adults as they are very rarely affected by acute OM and, even if this does occur, prompt diagnosis before transition to chronicity is often missed. On the contrary, in children, who are frequently affected by acute hematogenous OM, differentiating between acute and chronic types has practical implications regarding the treatment plan and final prognosis. This is mainly due to the fact that younger patients have the ability to resorb, at least to some degree, devitalized bone tissue, thereby removing foci of "biofilm type" of bacterial growth and potentiating the effectiveness of early-instituted antimicrobial treatment [6]. Additionally, the duration of this antimicrobial treatment differs between acute and chronic OM, with the acute form being treated with three to six weeks of specific antimicrobials targeted at identified pathogens after initial empiric formulations, and the chronic form being treated for up to six months with targeted antimicrobial therapy without initial empiric therapy [7]. This is due to the fact that certain pathophysiological changes that occur during the evolution of the inflammatory process (such as pus formation, reparative reaction, formation of involucrum and bone sequestration), which dictate the treatment plan and prognosis, are time-dependent [8]. Consequently, the differentiation between an acute and chronic form, especially in children, has important implications on the treatment plan.

Some authors do not utilize strict temporal criteria for defining OM. In 1970, Waldvogel et al. emphasized the difficulty in distinguishing between acute and chronic OM in terms of clinical course (type and duration of symptoms) or histologic findings [9,10]. They classified all cases as either "initial episodes" or "recurrences." An initial episode was thought of as representing an acute type of the disease spectrum, while recurrences represented chronic cases. They documented significantly higher treatment failures in "recurrences" as compared to the "initial episodes" for both hematogenous cases ($p = 0.003$) and those secondary to a contiguous focus of infection ($p = 0.0005$). The same definition of acute OM as "initial episode" was adopted by Lieu et al. in a retrospective study of 95 patients aged less than 17 years [11]. Fifty-five percent of them had been treated conservatively, while the remaining 45% had received combined treatment (antimicrobial therapy plus surgery). A recurrence rate of only 8.5% was documented. Other authors utilized a list of clinical, laboratory and imaging criteria to define acute OM in children and adolescents [12–14].

Various temporal thresholds have been used to define acute OM (Fig. 1). The shortest time threshold was one week, and was documented in three studies reporting on pediatric populations (584 children) [15–18]. The percentage of surgical intervention across all three studies ranged from 5.3% to 56%, and the recurrence rate of the infection ranged from 0 to 12% (pooled estimate of effect size for recurrence rate [random effects model]: 3.5%, 95% confidence interval (CI): 0.1 to 11.5%, with significant statistical heterogeneity: $I^2 = 87\%$). In one study, a sub classification of acute hematogenous OM was proposed into early-acute OM (diagnosed within 48 hours of onset in children over one year of age), late-acute OM (diagnosed at 5 days or more in children over 1 year of age) and neonate-infantile type [16]. The rationale for this classification was based on the findings of the study that the success rate of antimicrobial treatment was 92% for early-acute type versus 25% for late-acute OM. Another commonly-used threshold was two weeks and was utilized by studies reporting on either pediatric [19–21], adult [22] or mixed populations [23]. Two out of the three studies dealing with the pediatric population reported on the recurrence of the acute infection, which ranged from 0 to 7% (pooled estimate of effect size [random effects model]: 3.6%, 95% CI: 0.02 to 13%, $I^2 = 79\%$), with the rate of operative intervention ranging from 8 to 44% [19,20]. Finally, in one study reporting on open, infected bone wounds of the distal fibula/tibia, an acute infection was considered when the duration of open wound drainage was less than six weeks [24].

The definition of chronic OM is much more variable in the literature. Various lower limits of duration of symptoms exist, above which a chronic osseous infection is considered (Figs. 2 and 3). These range from at least a week in one study [17] to at least six months in three studies [25–27]. In-between, there are studies using the lower limits of two weeks [23], six weeks [24], one month [22] and two months [28]. However, in all studies the most consistent sign of chronicity of infection was bone sequestration. In a recent systematic review of the literature on the classification on the long bone OM the authors concluded that the terms acute/chronic OM are unreliable and do not influence the diagnostic workup or the principles of medical or surgical management [29].

Given the great variability of definitions for acute and chronic OM existing in the literature, we conclude that these terms are impractical in most cases as they lack accuracy in describing the underlying disease, and cannot dictate the treatment plan or predict prognosis. An exception to the above conclusion is the pediatric cases of acute OM due to the greater capacity of the younger patients to absorb necrotic bone and, therefore, to potentiate the effects of medical treatment. Additional variation in the treatment plan between acute and chronic forms of OM is in the duration of antimicrobial treatment. Lima et al. concluded that in acute cases patients should be given initial empiric antimicrobial treatment followed by targeted treatment for three to six weeks, while chronic cases require up to six months of targeted therapy [7].

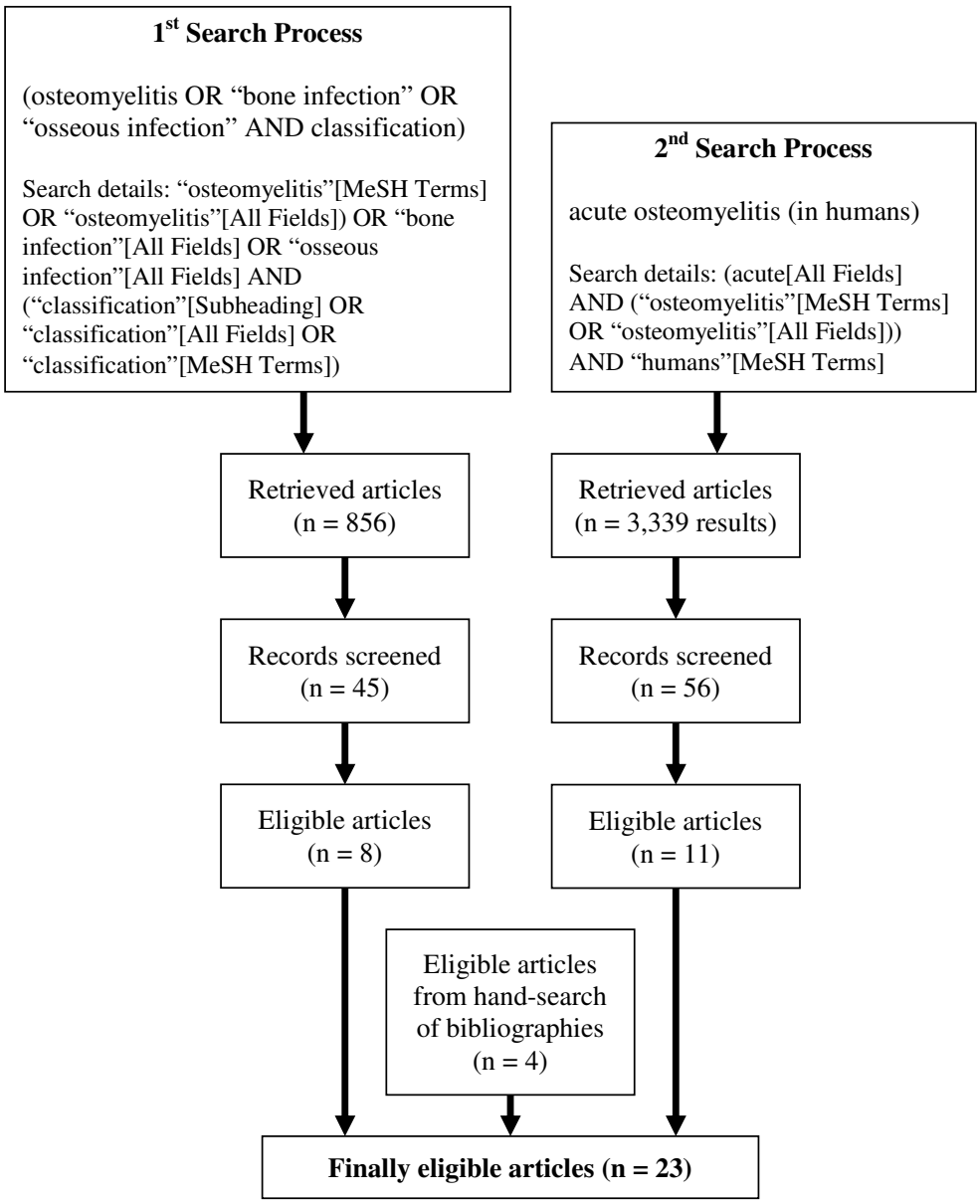

FIGURE 1. Search strategy flow chart.

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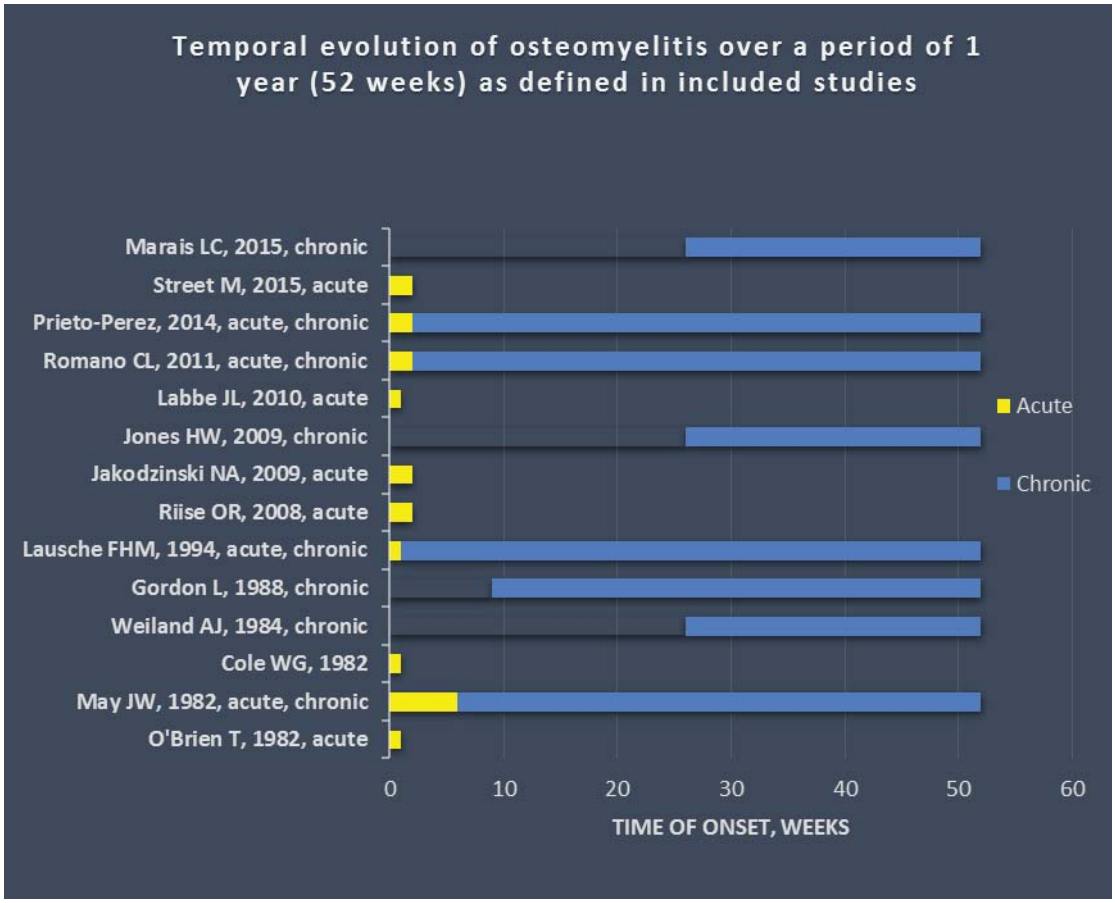

FIGURE 2. Temporal evolution of osteomyelitis over a period of one year as defined in included studies.

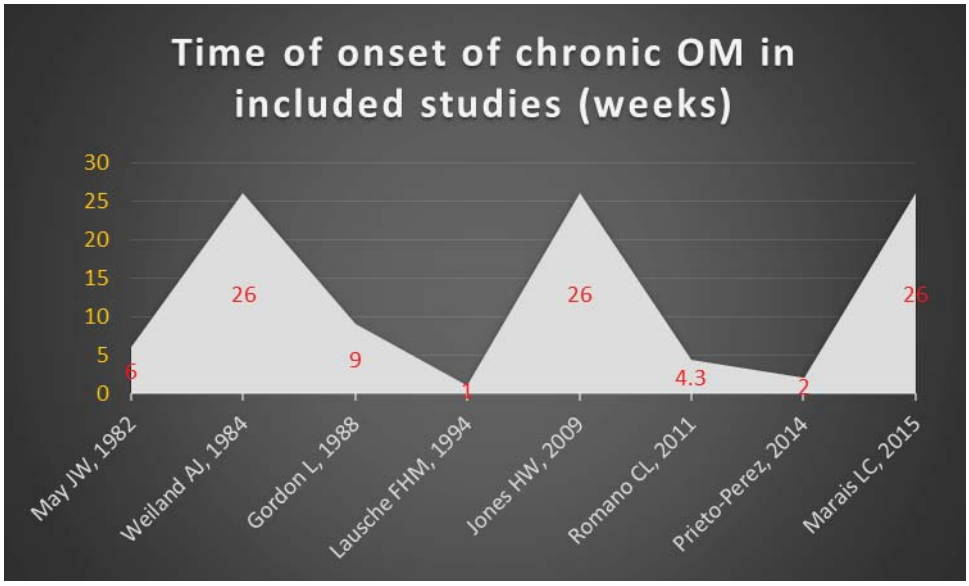

FIGURE 3. Time of onset (weeks) of chronic osteomyelitis, as defined in the included studies.

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QUESTION 5: Is synovial fluid or fracture hematoma always aseptic? If not, could this play a role in acute infection or periprosthetic joint infection (PJI) after open reduction and internal fixation (ORIF)?

RECOMMENDATION: Fracture hematoma is not always aseptic. It is unknown if synovial fluid is always aseptic. In addition, it is unclear if this plays a role in acute infection or fracture-related infection (FRI) after ORIF.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 5%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The association between soft-tissue conditions and infection has been well-known since the 1970s, when Gustilo and Anderson described how the major risk factor for post-traumatic infection following open fracture was the quality of the soft tissue envelope [1]. More recent evidence has demonstrated how traumatized host tissue can result in altered vascularization, decreased perfusion, increased endothelial permeability and decreased oxygenation; all of which can compromise the body's innate ability to resist local infection [1,2]. The prevailing theory of infection is that it is secondary to inoculation of pathologic microorganisms in traumatized tissues; however, it is unclear how infection occurs in closed trauma if there is no bacterial contamination through an open wound [2]. Some have questioned the common belief that synovial fluid and fracture hematoma is always aseptic based on evidence from other surgical fields that demonstrated how bacterial balance within presumably clean soft tissues affects the likelihood of soft tissue healing versus infection [3].

Two recent studies explored if fracture hematoma or callus was aseptic. In contrast to the prevailing view that these tissues are always clean, both studies found that 14 to 40% of the deep tissues grew bacteria when cultured, but no study has replicated these findings with synovial fluid. Szczesny et al. used conventional and molecular bacterial detection methods to determine if bacteria colonized lower limb soft tissues and bone following closed fractures in 71 patients. Cultures of fracture callus were positive in 26.7% of patients and bacterial rRNA was isolated in 41% of patients [4]. Similarly, Font-Vizcarra et al. evaluated the presence of positive cultures from hematoma in 109 patients with femoral neck fractures. They found that fracture hematoma was positive in 31.2% of all patients [2]. In both studies, the most common cultured organism was *S. epidermidis*. Based on recent basic science data, the presumed mechanism of infection of the deep tissues was that high-stress conditions resulted in decreased ability to contain skin and mucosal flora, leading to seeding of traumatized soft tissues/hematoma by lymphatic spread or transient bacteremia [1,2,4].

Although there is good evidence that fracture hematoma is not always aseptic, it remains unclear if the bacteria within the deep tissues play a role in acute infection or PJI after ORIF. Font-Vizcarra et al. did not find that culture positivity was a risk factor for early post-traumatic infection unless the specimen grew gram-negative rods [2]. Similarly, positive cultures from the fracture callus was not associated with non-union following closed tibia or femur fractures

[4]. Based on this data, it is unknown what bacterial load is necessary to evoke infection and overwhelm the host response [3].

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QUESTION 6: What is the relationship between implanted metal and colonization under a vacuum-assisted closure (VAC) in open fractures?

RECOMMENDATION: The use of negative pressure wound therapy (NPWT or VAC) over exposed orthopaedic implants has been reported but its role remains unknown. Furthermore, no evidence exists regarding the effect of NPWT on the colonization of metal implants in open fractures. Further research is required to provide more insight into this question.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

NPWT has emerged as a promising modality for the treatment of open fracture wounds between operative debridements and delayed wound closure or coverage [1,2]. Traditional management of fractures with soft tissue defects included wet-to-dry dressings with the risk of wound contamination and infection rates reportedly as high as 50% [3]. In addition to providing a semiocclusive dressing, NPWT mechanisms of action include stabilization of the wound environment, reduction of wound edema, improvement of tissue perfusion and stimulation of cells at the wound surface [1]. While initial randomized controlled trials (RCTs) favored NPWT in reducing infection in open fractures [4], a recent Cochrane database review found little difference compared to standard dressings [5]. The ability to successfully clear the infection may be tied to the VAC's effect on the wound bioburden [6].

A recent systematic review identified 24 studies investigating the topic of bacterial growth and NPWT, but none contained exposed implants [6]. The authors identified 10 experimental studies, 4 RCTs, 6 clinical studies and 4 using an instillation VAC system [6]. Of the RCTs, only one quantified bacterial proliferation and performed species analysis. Moues et al. found that NPWT selectively reduced non-fermentative gram-negative bacilli (NFGNB) but increased the proliferation of *S. aureus* [7]. The other three RCTs found no difference with the NPWT in regard to reduced bacterial growth or number of positive cultures [6]. The authors of this review concluded that there was a lack of concensus in the literature if the NPWT increases, decreases, or has no effect on the wound bioburden.

Perhaps even less is known about the relationship between implanted metal and colonization under a NPWT device in open fractures, as no studies have investigated this topic. The main reason is that contemporary "fix and flap" open fracture treatment does not advocate the use of NPWT devices over exposed metal. Some cases where this treatment might be an option include: (a) open fracture treated initially with hardware that undergoes wound breakdown, (b) if hardware removal at debridement is not feasible or would drastically compromise limb stability or (c) the patient is not a medical candidate for additional soft tissue coverage or additional surgery [8]. In such cases, the recommendation is to perform a secondary early coverage with local or distant flaps, but NPWT is not an option for definitive treatment. While case reports and small series have described the use of a wound VAC over exposed orthopaedic hardware in other instances [8–13], no studies have included bacterial proliferation or speciation analysis.

In conclusion, while there is evidence supporting the safety and efficacy of NPWT over exposed metal for a period of time without infectious complications, there are no published studies investigating this in associaton with open fractures. While the use of NPWT in open fractures with exposed metal is a viable option, it is not a part of the contemporary treatment of open fractures. Further research and study into implant colonization under a NPWT will be required before such a practice can be routinely recommended.

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Treatment

3.1. TREATMENT: ANTIBIOTICS AND NONOPERATIVE MANAGEMENT

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QUESTION 1: What is the most optimal prophylaxtic antibiotic coverage and treatment duration for open fractures of long bones?

RECOMMENDATION: The use of prophylactic antibiotics for open fractures of long bones has a protective effect against early infection. Antibiotics should be administered as soon as possible after the injury. The antibiotic of choice should target gram-positive organisms. Additional coverage for gram-negative organisms should be considered for patients with high-energy open fractures. Antibiotics should not be continued for more than 72 hours after wound closure.

LEVEL OF EVIDENCE:

- Efficacy of prophylactic antibiotics – Strong
- Timing of prophylactic antibiotics – Moderate
- Choice of antibiotics – Limited
- Treatment duration – Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Efficacy

Antibiotic administration has been shown to decrease the infection rate in open fractures in randomized controlled trials [1,2] as well as systematic reviews [3,4]. Patzakis et al. demonstrated for the first time the benefit of antibiotics in a prospective, randomized study [1], in which the infection rates for cephalothin versus penicillin with streptomycin versus no antibiotics were 2.3%, 9.7%, and 13.9%, respectively. In a Cochrane review data from 1,106 participants in eight studies were analyzed. The use of antibiotics had a protective effect against early infection compared with no antibiotics or placebo (risk ratio (RR) 0.43, 95% confidence interval (CI) 0.29 to 0.65, absolute risk reduction 0.07 [95% CI 0.03 to 0.10]). [3]. Another more recent systematic review also suggested a large, consistent reduction in infection risk with antibiotic use (RR 0.37, 95% CI, 0.21 to 0.66) [4].

Timing

In a retrospective study of type III open tibial fractures by Lack et al., administration of systemic antibiotics more than 66 minutes after injury was significantly and independently associated with deep infection (odds ratio (OR), 3.78, 95% CI, 1.16 to 12.31) [5].

Based on the quality and quantity of available evidence, the initial strength of the recommendation for early administration of antibiotics would be limited. However, we can upgrade this recommendation to one of moderate strength based on the following factors: (a) there is strong evidence that antibiotics need to be given and (b) delaying the necessary administration of antibiotics does not convey any benefit that could balance the potential risk of increased infection rate with delayed administration.

Choice of Antibiotics

Target organisms for prophylactic administration should be contaminants in the wound. Studies evaluating the microbiology of open fracture wounds have consistently shown that most contaminants are gram-positive organisms [6,7]. A study of 616 type I and II open fractures of the tibia reported that bacterial contamination at the fracture site consisted of a similar distribution of gram-positive (75 to 78%) and gram-negative (22 to 26%) species upon arrival at the emergency department, at the start of the operation, and at wound closure [6]. Methicillin-resistant *Staphylococcus aureus* (MRSA) were absent among the strains isolated at these stages [6].

The importance of antibiotics covering gram-positive organisms (usually a first-generation cephalosporin) is widely agreed upon. However, the necessity of coverage against gram-negative organisms or against anaerobes remains controversial.

No studies in the literature have directly compared gram-positive coverage to combined gram-positive and gram-negative coverage. Patzakis et al. recommended addition of aminoglycosides in all open fractures and reported a reduction in the infection rate from 14.6% in open tibias treated with a cephalosporin (from 1976 to 1977) to 4.5% in open tibias treated with both a cephalosporin and an aminoglycoside (1979 to 1980). However, this was not a direct comparison but instead a comparison of patients treated in different time periods in two prospective studies [8]. Gustilo et al. reported that 77% of cultures isolated from infected open fractures were of gram-negative bacteria and advocated addition of aminoglycosides for type III open fractures [9]. Similarly, Vasenius et al. in a randomized controlled trial of clindamycin vs. cloxacillin reported high surgical site infection (SSI) rates in type III open fractures and advocated addition of an aminoglycoside in these severe open tibia fractures [10].

Contamination of open fracture wounds with gram-negative organisms, although less frequent, still occurs [6,7] and a severe open fracture may be misclassified due to limitations in the interobserver agreement of the Gustilo-Anderson classification [11]. However, the SSI rates of Gustilo type I and II fractures have been consistently low in the literature even with narrow-spectrum antibiotics that mainly target gram-positive species [9].

Therefore, administration of a first-generation cephalosporin is recommended for Gustilo I and II fractures [12–14] and additional administration of an antibiotic with good gram-negative coverage is recommended in Gustilo type III (e.g., aminoglycoside or 3rd generation cephalosporins) [13,14,15,16]. Aminoglycosides may cause nephrotoxicity, especially in the setting of renal disease or dysfunction; therefore, renal function should be considered beforehand. Pannell et al. reported that gentamicin use during treatment of open fractures does not lead to increased rates of renal dysfunction when used in patients with normal baseline renal function [17]. Unfortunately, renal function is often not known at the time of initial admission of antibiotics.

Anaerobic coverage (e.g., penicillin, clindamycin or metronidazole) is recommended in the presence of potential clostridial contamination (e.g., fecal contamination or farm-related injuries) [13,14]. However, no study has compared anaerobic coverage in such injuries. A group developing guidelines for combat injuries that are severely injured and contaminated did not recommend anerobic coverage, but instead emphasized early and thorough debridement.

The emergence of antimicrobial resistance in bacteria has created concerns about the adequacy of current antibiotic protocols, especially against MRSA. However, a randomized controlled trial comparing vancomycin and cefazolin versus only cefazolin in 101 patients with open fractures found no difference in the infection rates between the groups: 19% in the group receiving vancomycin and cefazolin versus 15% in the cefazolin only group [18]. As a result, the routine use of vancomycin in open fractures cannot be recommended based on available data.

Duration

Two randomized controlled trials compared one to five days of antibiotics in the management of open fractures [6,19]. Both studies reported that the infection rates were similar in the one-day and the five-day groups and advocated against the prophylactic administration of antibiotics for five days. However, no randomized controlled studies have compared one-day, two-day, or three-day antibiotic prophylaxis. A retrospective case control study of 1,492 open fractures by Dunkel et al. showed after multivariate analysis that there was no significant difference in infection risk for one-day prophylaxis compared with longer regimens [20]. Although the OR for infection in the two/three-day group compared to the one-day group was 0.6 (95% CI, 0.2 to 2.0) in all fractures and 0.3 (95% CI, 0.1 to 3.3) in type III fractures. These lower ORs were not found to be significant.

Prolonged prophylactic administration of antibiotics beyond 72 hours is not recommended. In the absence of additional data for type I and II open fractures we would recommend administration of antibiotics for at least 24 hours after wound closure, but not to exceed 72 hours. In type III fractures we recommend 72 hours of antibiotic administration or 24 hours after closure or soft tissue coverage of the wound, in agreement with existing guidelines [13,15,16,21].

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QUESTION 2: What antibiotic(s) should be used for low-energy open fractures? What antibiotic(s) should be used for high-energy open and grossly-contaminated fractures?

RECOMMENDATION:

1. Antibiotic treatment targeting gram-positive organisms is recommended as soon as possible for all open fractures; low- and high-energy.
2. In high-energy or grossly-contaminated open fractures, additional antibiotics should be considered for gram-negative coverage.

LEVEL OF EVIDENCE: 1. Strong; 2. Limited

DELEGATE VOTE: Agree: 95%, Disagree: 0%, Abstain: 5% (Unanimous, Strongest Consensus)

RATIONALE

Open fractures are those that occur with associated skin and overlying soft tissue disruption, resulting in communication between the fracture site and the external environment [1]. The amount of energy imparted to an extremity during trauma results in a greater or lesser degree of bone and soft tissue compromise. Many authors have attempted to use different classifications to correlate the degree or amount of energy and the tissue compromise. The most commonly used is one described by Anderson et al. [2], later modified by Gustilo et al. [3]. For the purpose of this document, this definition will be used and correlated with the degree of energy associated. According to this classification, type I fractures are characterized by a wound of < 1 cm with minimal contamination, comminution and soft-tissue damage (these are low-energy). Type II features lacerations of > 1 cm and moderate soft- tissue injury, but wound coverage is adequate and periosteal stripping is not extensive (moderate energy). Type III fractures are divided into three subtypes and are all considered as high-energy. Type IIIA is characterized by high-energy trauma, extensive soft-tissue damage and substantial contamination, but wound coverage remains adequate after debridement has been completed. Type IIIB displays inadequate wound coverage following debridement and coverage procedures are required. Type IIIC is an open fracture associated with an arterial injury requiring repair.

One of the main purposes of this classification, besides description, is the correlation with infection rates which have been shown to increase correspondingly [4]. Rates of infection have been reported to range from 0% to 2% for type I, 2% to 5% for type II, 5% to 10% for type IIIA, 10% to 50% for type IIIB, and 25% to 60% for type IIIC3 [2,3,5]. Prophylactic antibiotics have become a standard for open fractures since 1974 when Patzakis et al. [6] demonstrated in his prospective study that cephalothin had significantly lowered the infection rate to 2.3 % compared with 13.9% in the control group. This finding was later confirmed by a systematic review demonstrating that the use of antibiotics had a protective effect against early infection compared with no antibiotics or placebo [7].

The efficacy of first-generation cephalosporins for open fractures has been confirmed in level I and II studies [7,8]. As initially reported by Gustilo et al. [3], type III fractures had a high rate of gram-negative infections, which supports the addition of an aminoglycoside or a third-generation cephalosporin. A different, prospective randomized study of severe open tibia fractures (type II and III) comparing first-generation cephalosporin and third-generation cephalosporin showed no statistical difference in the rate of infection [9]. *The Surgical Infection Society Guideline: Prophylactic Antibiotic Use in Open Fractures: an Evidence-Based Guideline* recommends the administration of first-generation cephalosporin for 24-48 hours preoperatively as a safe and effective prophylactic choice in patients with type I open fractures [10]. The *East Practice Management Guidelines Work Group: Update to Practice Management Guidelines for Prophylactic Antibiotic Use in Open Fractures* recommends that preoperative antibiotic prophylaxis for coverage of gram-positive organisms should begin for patients with open fractures as soon as possible after injury [11]. For type III fractures, additional coverage for gram-negative organisms may be given as these fractures are considered highly contaminated, although this aspect is not yet clearly supported by high-level studies [12].

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QUESTION 3: What is the optimal mechanism for delivery of local antibiotics in contaminated or infected wounds?

RECOMMENDATION: There is moderate evidence to support the use of local antibiotic delivery in contaminated or infected wounds. Future data collection seems important to improve our knowledge on this topic.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 75%, Disagree: 15%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

The evidence regarding the optimal mechanism for delivery of local antibiotics in contaminated or infected wounds is moderate. Open limb fractures are often associated with considerable bone damage including periosteal stripping, extensive soft-tissue trauma and severe contamination [1,2]. This enables bacteria to establish a fracture-related infection (FRI) by breaching the damaged skin barrier and adhering to non-living surfaces, such as implants or dead bone fragments [3]. FRI, which occurs up to 30% of cases after complex open fractures, is the one of the most significant complication after fracture fixation and is associated with a significant socio-economic impact [4,5]. Therefore, one of the main objectives in the management of open fractures is infection prevention [6]. Overall, current evidence on the local application of antibiotics in the prevention of FRI is limited. Moreover, comparative studies on local antibiotics and carriers are nonexistent.

With this in mind, a recent comprehensive literature search was performed in PubMed, Web-of-Science and Embase [7]. Cohort studies investigating the effect of additional local antibiotic prophylaxis compared to systemic prophylaxis alone in the management of open fractures were included and the data were pooled in a meta-analysis. Following screening and confirmation of eligibility, 18 articles were available for analysis. Further review of these studies revealed the absence of a control group in 10 case-series. Finally, eight studies [8–15] with a total of 2,738 patients were eligible for quantitative synthesis. The effect of antibiotic loaded polymethyl methacrylate (PMMA) beads was investigated by six [8–13] of these studies and two [14,15] studies evaluated the effect of local antibiotics applied without a carrier. Meta-analysis showed a significantly lower infection rate when local antibiotics were applied than in the control group receiving standard systemic antibiotic prophylaxis alone. This effect was present in all three main Gustilo-Anderson types. However, when evaluated by the 'Grading of Recommendations Assessment Development and Evaluation (GRADE)' approach, it appeared that these results should be interpreted with caution due to the low rating of the recommendation.

This low rating implies the uncertain impact of heterogeneity and bias on the pooled data results [16]. Most studies used PMMA as a carrier for application of local antibiotics. The studies by Henry et al. [8] and Ostermann et al. [9,10] found a beneficial effect of locally applied tobramycin PMMA beads. This finding was supported by Keating et al. who reported a trend towards reduced risk of FRI with the addition of local tobramycin-loaded PMMA beads [11]. Ziran et al. also investigated the effect of tobramycin-loaded PMMA beads and reported a two-fold risk reduction in infection rate (31.3% vs. 16.7%) [12]. However, due to the small sample size, the study is associated with a considerable risk of bias and its results should be interpreted with caution. Conversely, the only randomized control trial (RCT) in this meta-analysis did not find any beneficial effect in preventing FRI with the use of tobramycin-loaded PMMA beads and even reported an increased risk of FRI (8.3% vs. 5.3%). However, this study, conducted by Moehring et al., is associated with a considerable risk of bias due to patient prognostic factors not being reported, inadequate case matching with regards to Gustilo-Anderson type and the absence of a clearly defined primary outcome [13].

Two studies investigated the effect of local antibiotics without a carrier [14,15]. In open articular tibial fractures, Singh et al. found no beneficial effect of topical vancomycin, although this study is associated with a considerable risk of bias due to a small sample size, inadequate reporting of soft tissue involvement and length of follow-up [14]. The advantages of topical vancomycin include widespread availability, low costs, efficacy against most common pathogens and limited concerns regarding inhibition of bone healing or osteogenic cytotoxicity [17]. However, there are concerns that in the age of widespread antimicrobial resistance, the use of vancomycin should be reserved for therapeutic, rather than prophylactic, purposes [15].

Lawing et al. investigated the effect of locally injected aqueous aminoglycosides in open fractures in a methodologically well-designed observational trial. They found a significantly reduced infection rate (9.5%) compared to the control group (19.7%). There was no obvious evidence that local aminoglycosides were inhibiting bone healing since they were not associated with a higher non-union rate [15]. O'Toole et al. recognized the missing evidence of topical vancomycin in extremity fractures as well and recently published a study outline of a planned multicenter RCT investigating its effect on FRI [17]. A qualitative analysis was performed on the ten studies [18–27] that were excluded from the meta-analysis for a lack of control group. Five of these studies investigated the effect of PMMA containing tobramycin [19,20,27] or the combination of tobramycin and vancomycin [21,23] and reported an infection rate from 0% to 20.0%. Chaudhary et al. assessed the efficacy of gentamicin impregnated collagen fleece in the treatment of open fractures in a case-series of 31 patients and reported an infection rate of 16.1% [25]. Cai et al. observed no infection in 26 open long-bone fractures treated with local vancomycin loaded calcium-sulfate pellets [24]. Three series reported no deep infection after treating in total 22 open tibia fractures with a poly (D,L-Lactide) (PDLLA)/gentamicin coated tibial nail [18,22,26].

Overall, we can state that most evidence regarding local antibiotic carriers is limited to studies using local PMMA beads. Indeed, antibiotic impregnated PMMA beads should not be neglected in the acute management of open fractures. PMMA is non-biodegradable and therefore requires surgical removal, which limits its application to cases that need a planned second-look operation. In addition, following the initial high antibiotic level release from PMMA, there is a prolonged low-level antibiotic release that may be below minimum inhibitory concentration (MIC) for potential pathogenic

organisms. This might initiate a selection pressure that favors the emergence of resistant strains, as well as a foreign body reaction [28]. As mentioned earlier there were also studies included in this review that administered antibiotics without a carrier. The main disadvantage of locally administered antibiotics without a carrier is that there is no controlled delivery of antibiotics directly into target tissues and no sustained release over a sufficient time interval [28]. Biodegradable carriers overcome this issue and do not have the limitations of PMMA. New absorbable biocomposites, such as gentamicin-loaded calcium-sulfate/hydroxyapatite, have shown to be highly effective in treatment of chronic osteomyelitis [29]. Malizos et al. demonstrated in a recently-published multicenter RCT that a fast-resorbable antibiotic loaded hydrogel significantly reduced infection rates after internal osteosynthesis of closed fractures [30]. However, evidence in clinical literature on the effectiveness of degradable carriers in open fractures is limited. Our literature search identified only five case-series analyzing the effect of biodegradable antibiotic carriers in open fractures. Even though these studies are associated with a considerable risk of bias, the overall results are promising: no infections were reported in 26 open fractures treated with vancomycin loaded calcium-sulfate pellets [24] and in 22 open tibia fractures stabilized with a gentamicin coated tibial nail [18,22,26]. The study by Chaudhary et al. did report some infections with the use of antibiotic impregnated collagen fleece [25].

In conclusion, this systematic review is providing an overview of most recent literature on local antibiotic prophylaxis in open long-bone fractures, including various new absorbable carriers [28,30,31]. The beneficial effect of local antibiotics in open limb fractures was proven by pooling data exclusively from cohort studies that compared the effect of additional local antibiotics to standard systemic antibiotic prophylaxis. With respect to the type of carrier that should be used, most available evidence exists on antibiotic-loaded PMMA beads. As PMMA has potential downsides, multiple biodegradable carriers have been recently developed and some of the new carriers seem promising (e.g., poly [D,L-Lactide] [PDLLA]/gentamicin coating, fast-resorbable antibiotic loaded hydrogel). The main limitation of this review and meta-analysis is the low quality of evidence available in the literature. RCTs of sufficient statistical power and bias limiting methodologies are required to corroborate the findings of this meta-analysis. Of critical importance is the reporting of trials in accordance to agreed minimum datasets and, in particular, the use of a standardized definition for FRI [32].

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QUESTION 4: Is there a role for a combination of local and systemic antibiotic delivery systems to treat open fractures with overlying contaminated wounds?

RECOMMENDATION: The administration of systemic antibiotic and a local antibiotic delivery device (system) is an effective treatment strategy for open bone fractures with contaminated wounds.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 87%, Disagree: 4%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

The use of local antiseptic or antibiotic in the treatment of open bone fractures for infection prevention has a history of over 100 years, and this treatment approach continues today [1,2]. The use of systemic antibiotics for the treatment of open bone fractures is supported by landmark clinical studies by Patzakis, Harvey and Ivler, as well as Gustilo and Anderson [3,4]. Their early studies indicated that systemic antibiotic treatment was therapeutic and prophylactic in preventing wound infections in open bone fractures.

With the development of the addition of antibiotics, first in bone cement and later in other biomaterials, local antibiotic delivery for the treatment of open bone fractures became a therapeutic option for infection prevention [1,4–8]. While several recent reviews by Isaac et al., Warrender et al. and Gosselin et al. support the role of systemic antibiotic delivery in the treatment of open bone fractures [9–11], the 2014 systematic review by Craig et al. directly addresses the role of systemic and local antibiotic delivery in open tibia bone fractures [12]. Their study conclusion was,*"The findings support consideration of augmenting the antibiotic prophylaxis regimen to include locally delivered antibiotics. Patients with severe fractures will obtain greatest benefit from infections avoided"* [12]. Another key comment in the Craig et al. study conclusions is, *"No trial directly compared the two treatments for open tibia fractures, limiting the ability to attribute the differences in observed infection rates directly to the treatments themselves.* ***A large comparative study to improve the evidence on relative effect size is merited****"* [12]. A more recent meta-analysis by Morgenstern et al. concluded that there is a risk reduction with respect to infection of 11.9% if additional local antibiotics are given prophylactically for open limb fractures. Although the authors stated that due to limited quality, heterogeneity and considerable risk of bias, the pooling of data from primary studies has to be interpreted with caution [13].

Despite the lack of the mentioned direct comparison study and many other technical questions that range from antibiotic therapy duration to antibiotic selection, several retrospective studies do support the combination of systemic and local antibiotic delivery for infection prevention during the treatment of open bone fractures.

Limitations

- Used only English language journal articles for review

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QUESTION 5: What is the most optimal antibiotic treatment for chronic osteomyelitis?

RECOMMENDATION: Antiobiotic selection should be culture-specific, if possible. No clear evidence exists to suggest that longer duration of therapy (12 to 16 weeks) is superior to shorter duration (4 to 6 weeks). In addition, there is no evidence to support the proposition that intravenous (IV) antibiotic treatment is superior to oral treatment.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Chronic osteomyelitis remains a challenging problem in 2018. Recurrence of infection is common with a reported incidence of 20 to 30% [1,2]. The disease includes a vast spectrum of clinical scenarios that range from mandibular osteomyelitis arising as a result of dental complications, chronic vertebral osteomyelitis, post-surgical and post traumatic long bone osteomyelitis, pressure related chronic osteomyelitis of the pelvis, calcaneus and other sites as well as diabetic foot infections. Other disease processes also could be included in this group. Complicating the picture is the fact that these infections are caused by a multitude of pathogens and may be polymicrobial. Management of chronic osteomyelitis usually requires surgical debridement plus antibiotic therapy [3]. Because of variations in surgical approaches and the recent use of local antibiotic delivery devices, recent literature contains multiple variables that are difficult, if not impossible to control for, to determine what influence the systemic antibiotic played in the patient's outcome.

Antibiotic Choice

Older literature that includes randomized control trials (RCTs) often used an oral quinolone with a comparator parenteral agen [4–7]. Gentry and Rodriguez prospectively compared ciprofloxacin with cephalosporin or nafcillin plus aminoglycoside in 31 patients with biopsy proven osteomyelitis. These two populations had similar success rates of 77% and 79% respectively [4]. Mader et al. evaluated 26 patients with chronic osteomyelitis with oral ciprofloxacin vs. "standard parenteral therapy" consisting of nafcillin, clindamycin and gentamicin singularly or in combination. Both groups had similar success rates when evaluated two to three years after treatment [7]. Gentry and Rodriguez compared 19 patients with oral ofloxacin for 8 weeks with 14 patients with parenteral antibiotics for 4 weeks and found 74% and 86% success rates, respectively [5]. Gomis et al. evaluated 32 patients who had susceptible chronic osteomyelitis with oral oflaxacin versus imipenem-cilastin and found cure rates of 69% and 50%, respectively which were not statically significantly different [6]. Euba et al. compared 50 patients with Staphylococcal osteomyelitis comparing rifampin and clotrimoxazole combined versus IV cloxacillin for 6 weeks with oral cloxacillin for 2 weeks. Treatment outcomes in these two groups were similar and not statistically significantly different [8]. Norden et al. compared 19 patients with chronic post-traumatic chronic osteomyelitis using IV Nafcillin or cephalothin with IV nafcillin plus rifampin and found that cure rates were higher in the IV nafcillin plus rifampin group but this was not statistically different [9]. In the final RCT, Sheftel et al. studied ceftazidime vs. ticarcillin plus tobramycin for chronic gram-negative osteomyelitis in 18 patients and found cure rates of 67% and 89%, respectively [10].

Finally, Spellberg and Lipsky published a review of systemic antibiotic therapy for chronic osteomyelitis in Clinical Infectious Disease in 2012 [11]. Included in that summary were 49 non-RCTs that included 9 to 115 patients in each study with most studies having 20 to 40 patients each. The study populations were diverse and included patients with and without infected prostheses [11]. Surgical intervention was not universal in the studies and follow up was variable. Despite these limitations, some lessons can be learned. In the nonrandomized studies that included four to six weeks of a parenteral ß-lactam, the cure rates were 60-90% [1]. Cure rates were lower in patients that had chronic osteomyelitis with Pseudomonas [11]. Cure rates were also lower in studies where vancomycin was compared with ß-lactam agents for osteomyelitis caused by *S. aureus* [11]. Fluoroquinolones were the best studied antibiotic group for chronic osteomyelitis. Most studies reported cure rates of 60-80% [11]. Rifampin also improved outcomes in several studies when combined with fluoroquinolones and other active agents for chronic *S. aureus* osteomyelitis [11]. However, because of the numerous drug interactions with rifampin, there are times when it is not advisable to use rifampin. In addition, rifampin should never be used without another known active agent due to the rapid development of rifampin resistance that often occurs within just a few days. Regardless, the authors of this review were unable to recommend the best agent for treatment [11].

Duration of Administration

Traditionally, six weeks of parenteral antibiotic therapy was prescribed for chronic osteomyelitis combined with surgical debridement [12,13]. Yet there is no clear advantage in the literature that longer durations result in better treatment success than shorter durations. In a recent systematic review, most of the included antibiotic therapy that was given was high-dose and administered for 12 to 16 weeks [11]. However, the available data in these studies is inconclusive to know if the higher doses or prolonged therapy improved outcomes [11]. At this time, the literature does not offer adequate evidence to determine the optimal duration of antibiotic therapy for chronic osteomyelitis [2,11,14,15].

Route of Administration

Recent evidence has shown that oral antibiotic therapy may be equally as effective as parenteral antibiotic therapy [2,11,15]. Conterno et al. conducted a Cochrane systematic review on antibiotics for treatment of chronic osteomyelitis in adults [2]. This review included RCT or quasi-RCTs regarding antibiotic treatment used after surgical debridement of chronic osteomyelitis in adults. They found no difference between oral and parenteral antibiotic therapy. This review was an update of a prior 2009 Cochrane review [16]. They concluded that the quality of evidence available was limited to make a definitive conclusion regarding antibiotic treatment of osteo-

myelitis [2]. In the aforementioned review, Spellberg and Lipsky suggested that chronic osteomyelitis can be effectively treated based on the antibiotic susceptibility of the pathogen(s) and pharmacokinetics with oral antibiotics as well as parenteral therapy. They concluded that oral antibiotic therapy with the proper agent was an effective alternative to parenteral antibiotics [11].

Conclusion

While the studies to date do not provide a clear optimal antibiotic choice, duration or route of administration for the treatment of chronic osteomyelitis, some observations are consistent from the data available. First, knowing the pathogen, pathogen sensitivities, antibiotic bone penetration and antibiotic toxicities do help the treating physician make the best choice for a specific patient and clinical scenario. It is important, whenever possible, to establish a microbiological diagnosis (or at least to obtain adequate bone tissue for culture in the lab) prior to initiating antibiotics. As the current recommendation for duration of therapy is typically 4-12 weeks, antibiotic exposure and toxicity can be significant. Second, in certain situations, oral therapy is just as effective as parenteral therapy and there are more studies supporting oral therapy than parenteral therapy. There is sufficient data to support the use of an active oral fluoroquinolone for osteomyelitis caused by gram-negative organisms, the use of an active fluoroquinolone with rifampin for *S. aureus* osteomyelitis, and the consideration of using trimethoprim-sulfa with rifampin for *S. aureus* osteomyelitis if both agents are active. Using an active fluoroquinolone alone for *S. aureus* osteomyelitis should be avoided due to the development of resistance while on monotherapy and the higher rate of relapse after therapy is completed. Third, adding rifampin to a variety of antibiotics seems to improve cure rates when coupled with another known active agent when treating *S. aureus* osteomyelitis. Fourth, surgical debridement and removal of infected hardware, when possible, generally improves treatment outcomes. Fifth, oral clindamycin which is routinely used for the treatment of acute *S. aureus* osteomyelitis in children [17–20], has not been well studied for the treatment of chronic osteomyelitis in adults. Finally, it is also important to keep in mind that antibiotics are only effective when they reach the site of infection. Adequate vascularized soft tissue coverage of infected bone, debridement of any significant necrotic tissue and sequestrum, and adequacy of blood flow to the affected site are likely critical factors in improving outcomes.

Clearly, additional RCTs are needed to answer the question regarding the optimal agent, route and duration of therapy for treating chronic osteomyelitis in adults.

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QUESTION 6: What is the recommended suppressive antibiotic therapy for the treatment of chronic osteomyelitis after fracture fixation when the implant cannot be removed?

RECOMMENDATION: Suppressive therapy with culture-specific antibiotics is aimed at allowing fracture healing prior to implant removal and definitive infection management.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infection after surgical treatment of fractures is a complication with significant morbidity, and in rare cases even mortality. Infections have often been classified according to the time interval between surgery and occurrence, although the distinction between acute and chronic infections has recently been challenged. Early infections are mainly caused by virulent microorganisms, such as *Staphylococcus aureus*, and diagnosed within the first three weeks of surgery. Delayed infections are typically due to less virulent bacteria, such as coagulase-negative Staphylococci, and develop between 3 and 10 weeks. Finally, late infections, occur after 10 weeks and are either caused by haematogenous seeding or by recurrence of inadequately-treated early infection [1]. Infections that occur following open reduction internal fixation (ORIF) are typically caused by biofilm-forming bacteria, which adhere to the implants [2]. In approximately one week, a mature biofilm already forming, which makes it less likely to for antibiotics alone to eradicate bacteria [3].

Common treatment for implant-related infection obeys to three established principles: surgical debridement, antibiotic therapy and eventual implant removal or staged exchange. However, in ORIF and with fracture-related infection (FRI), implant removal is unsuitable because of resulting fracture instability that often leads to prolonged infection [4,5]. This has consequences for the other aspects of treatment – if the implant is retained, the biofilm remains. Surgical debridement can remove the bulk of the bacterial load, but adjuvant antibiotic therapy must be directed towards the biofilm present. If the implants are retained, treatment consists of thorough surgical debridement, tissue cultures and long-term antibiotic suppressive therapy with rifampin-based combination antibiotic therapy. To date, only two classes of drugs have shown the properties that are needed for control of biofilm forming bacteria. Rifampin and other rifamycins act on biofilm active Staphylococci [6–11] and fluoroquinolones on gram-negative bacilli [12,13].

In the event of retained hardware after debridement of an acute infection following ORIF, the recommended antibiotic combination therapy should start immediately after the first surgical intervention and consists of 10 days of intravenous (IV) vancomycin and rifampin. Vancomycin was the agent of choice for empirical therapy because of its activity against a broad spectrum of microorganisms, the high incidence of gram-positive infections and the synergetic effect with rifampin [14–16]. Vancomycin therapy was started twice daily (1,000 mg IV), and was adjusted to maintain serum levels between 15 and 20 mcg/ml. Rifampin was given twice daily (450 mg IV). After tissue cultures identify the responsible bacterial pathogens and susceptibility data becomes available, vancomycin therapy can be switched to another, narrow spectrum antibiotic as indicated. Rifampin is continued unless rifampin-resistant bacteria are found.

Zimmerli et al. [2,6] assessed the effectiveness of this protocol in a randomized controlled trial, and after the IV administration period, oral combination antibiotic therapy with rifampin was continued for ten additional weeks. They reported 100% success in cases where both antibiotics were administered compared to 58% success when only ciprofloxacin was received. Barberan et al. [17] and Drancourt et al. [18] also studied infection following ORIF and evaluatied the effect of antibiotic combination therapy with rifampin reporting good results. Drancourt et al. [18] analyzed both periprosthetic joint infection (PJI) and FRI treated with initial retention and combination antibiotic therapy, and reported a success rate of 48% after an average follow-up of 23.5 months. The study of Barberan et al. [17] only included patients with infections following ORIF and demonstrated a success rate of 72%. In a prospective observational cohort study, Tschudin-Sutter et al. [19] analyzed 233 patients with orthopaedic implant-related infections of which 52.4% (122/233) were infections related to ORIF, for which the success rate was 90.2% (110/122) with the use of rifampin-combination regimen as suppressive therapy. This was seen on patients with implant retention after two years of followup. Patients were identified for inclusion using strict selection criteria (the duration of clinical symptoms was no longer than three weeks): stable implant, intact soft tissues, no abscess or sinus tract and the causative pathogen was susceptible to antibiotics with activity against surface-adhering microorganisms (i.e., rifampin for *S. aureus* or coagulase-negative Staphylococci and ciprofloxacin for gram-negative pathogens) [19]. This is so far the largest study evaluating patients with implant-associated infection managed with retention and long-term suppressive antibiotic therapy.

It is important to highlight the critical aspect of implant stability, as loose implants cannot be retained even if infection becomes evident at very early stages. Worlock et al. [4] demonstrated in a rabbit model that unstable tibial fractures were associated with significantly higher rates of osteomyelitis than those which were stable. These implants can often be retained when an acute infection develops after fracture fixation. Implant removal is generally undesirable in cases of acute infection as ORIF serves two different goals. First, the stability achieved by fixation is critical for fracture healing. When conditions are created in which micromotion between bone fragments is possible, resorption and necrosis of the affected bone will occur [5]. Second, the aim of operative fracture management and early mobilization is to prevent loss of function due to scarring of the surrounding soft tissue or joint stiffness. Special consideration should be given to infections after intramedullary fixation, with the popular belief that eradication of the infection is not feasible without implant exchange [20]. Chen et al. [21] reported on 23 infections following intramedullary (IM) nailing of the femur for fractures. The patients were divided into two groups where one group with IM nails had their nails removed and an external fixator was placed. All femur fractures with retained IM nails healed (12/12) and were infection free at followup of average 25 months. Only 7 of 11 patients (64%) in the external fixator group healed. Whereas removal or exchange of the implant provides the opportunity to remove the biofilm and thus reduce the bacterial load, in cases of implant retention the surgical debridement and adjuvant antibiotic therapy play a more important role.

In conclusion, in the situation of FRI where debridement and implant retention is chosen as the treatment strategy, rifampin (rifamycins) can be an effective adjuvant agent in suppressing gram-positive organisms while ciprofloxacin (fluoroquinolones) can be effective in suppressing gram-negative organisms.

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QUESTION 7: Is there a role for hyperbaric oxygen therapy (HBOT) and other non-antibiotic methods for the treatment of chronic osteomyelitis/implant infections?

RECOMMENDATION: There is limited evidence for the efficacy of hyperbaric oxygen (HBO) in the treatment of post-traumatic bone infections.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 5%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

HBOT has been proposed as an adjunctive therapy in the management of refractory osteomyelitis, which was defined as chronic osteomyelitis that persists or recurs after appropriate interventions have been performed or where acute osteomyelitis has not responded to accepted management techniques [1]. The procedure involves the intermittent inhalation of 100% oxygen in chambers pressurized above one atmosphere absolute (typically to about 2 to 2.5 atmosphere absolute (ATA)). It is based on the premise that increased tissue oxygen levels will enhance healing. Although adverse events are typically self-limiting, more serious potential complications include baro-traumatic otitis, pneumothorax, myopia and seizures [2].

While initially there was some enthusiasm about the use of HBOT in refractory osteomyelitis, this appears to have waned with only one case series published since 2004 [3]. Prior to this, a small number of descriptive studies were published that reported encouraging results [4,5]. A systematic review by Goldman in 2009 examined the evidence for HBOT in wound healing and limb salvage. Five studies were classified as "moderate" strength evidence (the remaining 10 being either "low" or "very low") [6]. In the first of these Morrey et al., reported on the outcomes of HBOT in 40 patients who had recurrent infection for more than 6 months after at least 1 surgical procedure [7]. Following surgery, antibiotics and HBOT, 85% of patients were reported to be disease-free at one year.

Davis et al. performed a retrospective study on 38 patients with actively draining wounds and at least 1 failed previous surgical procedure [8]. Complete healing was achieved, again in combination with surgery and antibiotics, in 89% of cases. From 1998 to 2004 Chen et al., published three overlapping case series involving patients who presented with recurrence of infection following prior surgical treatment [9–11]. The success rate of standard treatment, involving aggressive debridement, antibiotics and HBOT, was reported as 79% to 92% (note that the 2003 study was not included in the Goldstein systematic review). The findings from all of these non-comparative studies are however difficult to interpret and confounded by the fact that HBO was used as part of a multi-modal treatment strategy. Furthermore, it is not clear if the initial failed surgical procedures were performed by experienced musculoskeletal infection surgeons. There was only one comparative study included in the Goldman systematic review. Esterhai et al. performed a prospective non-randomized controlled trial and found that HBOT had no effect on length of hospitalization, initial clinical outcome or the late recurrence of infection [12]. The only clinical study published since the systematic review in 2009, described the experience of a single center with HBOT in general and did not provide a detailed description specific to the chronic refractory osteomyelitis patients [3].

Recently, the effect of HBOT on implant-associated infection was further drawn into question. Büren et al. illustrated in a standardized murine model that HBOT did not have a beneficial effect on the local infection or the immune response to the infection compared to standard therapy alone [13]. Interestingly, they also noted delayed bone healing and a higher rate of non-unions at 28 days in the HBOT group. Ultimately, there is currently only limited evidence

supporting the use of HBOT in post-traumatic infections and the single study with a control arm reported no benefit.

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3.2. TREATMENT: SURGEON AND CARE TEAM

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QUESTION 1: Should all infected non-unions be treated in specialized septic centers?

RECOMMENDATION: The current literature, although rich in case series and observational studies, does not lend support to the recommendation that "specialized septic surgery centers" should care for infected non-unions. However, because of the complexities of infected non-unions, care in specialized centers may yield the best possible outcome.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 70%, Disagree: 21%, Abstain: 9% (Super Majority, Weak Consensus)

RATIONALE

Infected nonunion is the persistence of an infection at the fracture site and the surrounding tissue and failure of bone healing for eight months, (U.S. Food and Drug Administration). It could be considered as an osteomyelitis at an unstable fracture before the debridement and which remains unstable thereafter. It is commonly accompanied by soft tissue problems, adjacent joint stiffness, motor and sensory dysfunction of the limb, chronic pain, depression and unrelated medical problems leading to considerable physical, social, financial and mental impact on the life of the patient and the healthcare systems and may even become a limb-threatening complication.

Bone healing and eradication of the infection is the main but not the only objective because a non-functional and deformed limb with pain and stiffness of the adjacent joints will be an unsatisfactory outcome even if at some point the bone heals sufficiently. Treatment is aimed at returning the extremity and the patient to the fullest function possible during and after the treatment process. This process is usually long-lasting and must be planned accordingly so that in case of failure, further treatment alternatives remain available. Because of the various nonunion types and the multitude of possible problems related to the patient's health and comorbidity, such as prior treatments and the bone and soft tissue defects, no simple treatment algorithms are possible. The recommended strategy, with an array of management alternatives, is: (a) the "infection-elimination first" by local radical debridement of all pathological tissue, followed by (b) tissue and bone reconstruction and (c) targeted chemotherapy with local and systemic antibiotics.

A specialized team of orthopaedic surgeons with expertise in a broad spectrum of techniques must thoroughly evaluate the patient and carefully consider all available information about the general health status and the local tissue conditions. The prior failed treatments must be taken into account, as well as the optimization of all treatment modifiers. Where extensive surgical exposures have failed consideration is given to less invasive techniques that respect the surrounding soft tissues. Stable fixation, adequate vascularity, bone-to-bone contact, and bone grafting or strong bone regenerate are crucial factors for success. The potential need for future treatment should be considered when pursuing any particular intervention.

The care of the patients with infected nonunions may be best performed at specialized septic surgery centers with an expert team approach to achieve the ultimate goals of bony union and restoration of alignment and function, while limiting the extent of residual disability. A medical center that treats infected nonunions should provide all of the appropriate resources and a supportive team of consulting specialists to contribute to all aspects of care, both at the initial evaluation and throughout the course of treatment. The role of anesthesiologists is obvious as well as of the internists for patients with serious medical conditions. Plastic surgeons are often necessary to reconstruct the soft tissues

after serial debridement and vascular surgeons may be required if the vascularity of the limb is in question. A multidisciplinary treatment team should be utilized in providing comprehensive care, including a pain management specialist, a psychiatrist to support patients with clinical depression, a neurologist to evaluate motor or sensory loss, a dietician to optimize the nutritional status, and physical and occupational therapists to facilitate rehabilitation. Microbiology and histopathology labs with the availability of modern diagnostic facilities, an experienced clinical pharmacologist and an infectious disease specialist are all integral parts of the multidisciplinary unit as well.

APPENDIX - SEARCH STRATEGY

There is no study in the literature that has evaluated this particular issue. We have conducted a broad literature search trying to identify articles or parameters that could lead us to musculoskeletal infection specialist centers, although the number of true, dedicated centers with multi-disciplinary units at this time remains very low. Medline, Cochrane, and Embase databases were searched, employing the terms: "infected nonunions," "septic nonunions," "specialist's septic centers," "infected nonunion AND hospital" and "infected nonunion AND septic center." After removing papers that did not match our criteria we ended up with 69 articles, which were all observational case series for infected nonunions. Out of those we identified 28 articles (all level IV) that could be used for our analysis. Hospitals with level I trauma centers that had a minimum of two publications about infected nonunions were classified as "specialist centers" (group A) [1–15]. Orthopaedic departments with only one publication were categorized as "non specialized septic centers" (group B) [16–28].

In total, there were 15 publications from 10 centers in group A, and 13 publications from an equal number of centers in group B. Regarding the different treatment methods, in group A, 60% reported using external fixator to stabilize the nonunion, 20% used open reduction and internal fixation (ORIF), 6% intramedullary (IM) nailing and the remaining used more than one technique. In 67% of the patients in group A a bone graft was used, whereas in group B only 38% mention using bone grafting. For the fixation of the bone in group B, in 54% external fixation were applied, 15% used IM nails, 7.7% ORIF, while the rest report the use of more than one technique (external fixators and plates). Most studies do not report the length of hospital stay and time for return to work. In addition, not all of them give data about limb shortening and alignment. The average number of patients in the studies was relatively small. Given also the heterogeneity of anatomical locations of the nonunions among the different studies, valid comparisons are not possible. The number of previous operations was comparable: 2.9 in group A, and 3.1 in group B.

In 54% of group A centers, the infected nonunions were treated in one stage and 46% in two stages. In group B, 73% of the patients were treated in one stage and 27% in two stages. Thirteen studies analyzed the outcomes of treatment with the Ilizarov method, nine studies analyzed the management with a single-stage or two-stage approach and use of cancellous bone grafting, three studies involved vascularized bone grafting, and one study involved a bulk allograft. Follow-up was higher in group A (46.4 months) compared to group B (37.3 months). Both groups demonstrated similar outcomes with respect to the elimination of infection. However, parameters such as length of hospital stay, time to bone healing, time until return to work, functional outcomes and patient reported outcome measures are not available, thus markedly limiting the strength of the recommendation.

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Authors: Vicky Gutierrez, Gerard Chang

QUESTION 2: Is there a minimum number of complex osteomyelitis procedures a surgeon should perform annually to ensure proper outcomes?

RECOMMENDATION: There is no literature supporting a minimum number of complex osteomyelitis procedures a surgeon should perform annually to ensure proper outcomes. Higher-volume referral centers, centers of excellence and multidisciplinary teams for the treatment of complex osteomyelitis may result in improved outcomes.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 76%, Disagree: 14%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

In the literature reviewed, there is no evidence to answer the question. Osteomyelitis is a complex pathology, which needs years of follow-up to be able to demonstrate the sustained remission of the disease. Osteomyelitis has multiple etiologies: 19% hematogenous, 47% secondary to a contiguous focus and 34 % due to vascular insufficiency [1]. There is no evidence to establish the optimal duration of treatment and many studies do not present good-quality data and include a small number of patients [1,2]. Therefore, most of the recommendations for the treatment of osteomyelitis is based on expert opinions.

In joint arthroplasty, high-volume centers, multidisciplinary teams and centers of excellence have been shown to improve patient outcomes with respect to the treatment of prosthetic joint infections [3]. In trauma, there have been few studies looking at the benefit of high-volume centers for the treatment of complex osteomyelitis and septic nonunions. Bauer et al. retrospectively evaluated the results of a French referral center for complex bone infections. They had 55 patients over the course of 10 years who were treated for infected non-unions of the tibia or femur. They showed that 89% of patients with an infected tibial or femoral non-union treated by a team specialized in complex bone and joint infections using a standardized surgical protocol had bone union and healing of the infection in an average of nine months [4]. In a similar study, Bose et al. reported on 67 long bone infected non-unions over 6 years treated by a multidisciplinary team. They found that 59/67 (88%) went on to fracture union and eradication of their infection [5]. Lastly, Salvana et al. treated 82 patients over 7 years with chronic osteomyelitis with an integrated team approach and found successful union and limb salvage in 77 (94%) cases [6]. In these three studies, the centers treated on average 6-12 cases of complex osteomyelitis per year. At this time there is no data supporting a minimum number of cases of complex osteomyelitis a surgeon should perform annually to ensure good results, but having greater experience collectively at an institution or within a dedicated unit would presumably results in the greatest likelihood of a successful outcome in this difficult cohort of patients.

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Authors: Willem-Jan Metsemakers, Jaime A. Leal

QUESTION 3: Who are the essential members of the multidisciplinary team required to manage infected fractures and non-unions?

RECOMMENDATION: The essential members of the multidisciplinary team managing infected fractures and non-unions require expertise in bone reconstruction, soft tissue reconstruction, microbiology, antibiotic treatment and advanced imaging. It is important to note that the exact members of the group and other specialists required will eventually depend on patient needs and local preferences.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

There is increasing evidence that teamwork and collaboration among healthcare workers are essential to improving patient outcomes [1,2]. Therefore, it is important to implement a multidisciplinary approach in treatment algorithms of fracture-related infec-

tions (FRI). The use of an antibiotic stewardship program is already a well-known concept for the management of different infection-related entities. These are defined as coordinated interventions designed to improve and measure the appropriate use of antibiotic agents by promoting selection of the optimal regimen, including dosing, duration of therapy and route of administration [3]. With its multidisciplinary approach, an antibiotic stewardship program improves patient safety and outcomes, and when combined with reduced readmission rates, reduces healthcare costs without compromising the quality of care [4–6]. Rodriguez et al. evaluated an evidence-based protocol for antibiotic prophylaxis in open fractures [7]. They demonstrated a short course of narrow-spectrum antibiotics (avoiding the use of broad-spectrum aminoglycosides and glycopeptides) does not increase the risk of soft tissue and skin infections after an open fracture.

Following the Infectious Diseases Society of America guidelines, infectious disease (ID) physicians and clinical pharmacists are the core members of antibiotic stewardship programs, but microbiologists and the implementation of administrative and information technology can also be of great importance [8]. However, as recently stated by Pulcini et al. [9], the composition of these teams is flexible and should be based on existing international recommendations and adapted to the local context based on resources available. Regarding the multidisciplinary approach to FRI, the treatment is based on two pillars: surgical management and clinical management.

Where the surgical management plays an important role, it seems imperative that surgeons (including musculoskeletal trauma surgeons and plastic surgeons) act as central members. Nevertheless, studies within this field are scarce. A multidisciplinary approach, which is constituted of collaboration between musculoskeletal trauma surgeons, the hospital's infection control department, nurses and anesthesiologists as primary team members, has been described to guide FRI prevention strategies [8].

With respect to treatment of FRI, a recent systematic review by Bezstarosti et al. (unpublished data) showed that out of the 93 included studies conducted between 1990 and 2017, only 12 studies (13%) discussed the members that were involved in their multidisciplinary team, with a wide variety of team members available: musculoskeletal trauma surgeons (10 studies), plastic surgeons (5 studies), ID physicians (5 studies), pharmacists (1 study), radiologists (1 study) and not further specified members (3 studies) [10–21]. A study by Bose et al. [12] obtained good results with a multidisciplinary team comprised of orthopaedic surgeons, plastic surgeons, radiologists and ID physicians for treating patients with infected nonunions of long bones [12]. It is important to note that most of the above-mentioned treatment studies focused on chronic/late FRI patients. A study by Dudareva et al. [22] reported a multidisciplinary approach allowed for successful treatment in the majority of cases with osteomyelitis of pelvic bones. The team members in this study were comprised of orthopaedic surgeons, plastic surgeons, and ID physicians. The team was completed by the contribution of specialized nurses, physiotherapists, occupational therapists and musculoskeletal radiologists.

In conclusion, although data specifically focusing on FRI is scarce, a collaboration of different specialties most likely would improve the outcomes in this difficult patient population. No study has evaluated the specific essential participants, but do mention the results with involved members. Antibiotic stewardship programs have already proven their use by means of a multidisciplinary collaboration between ID specialists, clinical pharmacists and microbiologists. The same approach should be applied to set up a main treatment plan for the FRI patient, including surgical, antibiotic and clinical aspects.

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3.3. TREATMENT: RISK FACTORS

Authors: Paddy Kenny, Giedrius Kvederas, John Gibbons

QUESTION 1: What are predictors of the need for allogeneic blood transfusion (ABT) in periprosthetic fractures?

RECOMMENDATION: Predicting factors for allogeneic blood transfusion are: revision arthroplasty, preoperative anemia, increasing age, higher comorbidity index, lower Body Mass Index (BMI), female gender, longer surgical time and hip surgery.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 95%, Disagree: 5%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

There is little data regarding predictors of the need for ABT in periprosthetic fractures. Periprosthetic fracture studies typically include a low number of patients, and conclusions about covariates are often not available. These fractures may be treated by either revision surgery or open reduction and internal fixation (ORIF). General indications for ABT in total joint arthroplasty (TJA) can be identical in the first group.

Slover et al. demonstrated that hip arthroplasty had a significantly higher likelihood of blood transfusion (odds ratio (OR) 1.76, 95% confidence interval (CI), 1.68 to 1.83) than knee arthroplasty. Increasing age (age ≥ 80 years; OR, 2.99, 95% CI, 2.82 to 3.17), Medicaid insurance (OR, 1.36, 95% CI, 1.27 to 1.45), higher comorbidity index (score of ≥ 3, OR, 2.33, 95% CI, 2.22 to 2.45), and females (OR, 1.75, 95% CI, 1.70 to 1.80) all had significantly higher odds of blood transfusion after TJA [1].

Parvizi et al., reported that advanced age, low BMI, simultaneous bilateral arthroplasty and low preoperative hemoglobin were independently associated with increased rates of ABT [2].

In a study by Rasouli et al., one-stage bilateral TJA (OR, 3.30;, 95% CI, 3.24 to 3.37; $p < 0.001$), anemia due to chronic blood loss (OR, 2.69, 95% CI, 2.59 to 2.74, $p < 0.001$), deficiency anemia (OR, 2.59; 95% CI, 2.56-2.62; $p < 0.001$) and increased Charlson comorbidity index (OR, 1.24, 95% CI, 1.23 to 1.24; $p < 0.001$) were independent predictors of allogeneic blood transfusion [3].

In the study by Solon et al., 12 patients with Vancouver B2 periprosthetic fractures around cemented collarless polished tapered (CCPT) stems treated by ORIF alone (median follow-up 67 months) were compared with those of nine patients with a similar fracture treated by revision surgery. All 12 patients with Vancouver B2 femoral fractures around CCPT stems treated by ORIF alone healed and all stems restabilized and remained stable within their original cement mantle. These patients had significantly shorter surgical times ($p = 0.002$) and required fewer units of blood transfusion ($p = 0.008$) than patients in the revision cohort [4].

Saidi et al. evaluated 3 different surgical methods for treating comminuted distal femoral periprosthetic fractures in 23 patients over the age of 70 (average age 80, range 70-90). Reconstruction techniques included seven allograft prosthesis composites (APC), nine revision systems (RSA), and seven distal femur replacements (DFR). Operative time and blood loss were found to be significantly less in RSA and DFR patients compared to the APC patients [5], suggesting that more ABTs are required in complex revisions for periprosthetic fractures [5].

Min et al. retrospectively evaluated the clinical and radiographic outcomes of a series of 21 Vancouver type B1 periprosthetic femur fractures (PPF) treated with minimally invasive plate osteosynthesis (MIPO) and locking compression plate (LCP) between February 2011 and February 2017. The mean duration of follow-up was 33.8 months. They also compared outcomes of these patients to similar patients with 19 Vancouver type B1 fractures treated with ORIF between April 2006 and December 2011. The authors found that operative time was significantly shorter and intraoperative blood loss was significantly less in the MIPO group compared to the ORIF group [6].

Fulkerson et al., showed that percutaneous fixation of PPFs with the Less Invasive Skeletal Stabilization (LISS) plate is an effective although technically demanding method of treatment with minimal blood loss [7]. Thomas et al. also had similar results with the LISS plate [8].

Blood loss was minimal and only two of ten patients needed a blood transfusion with Vancouver type B1 fractures treated with percutaneous cerclage wiring for fracture reduction and maintenance of reduction with MIPO utilizing an LCP [9].

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Author: Arjun Saxena

QUESTION 2: Is acute femoral neck fracture a risk factor for infection in patients undergoing hip arthroplasty?

RECOMMENDATION: There appears to be a higher incidence of infection in patients undergoing arthroplasty for acute femoral neck fracture compared to hip arthroplasty for primary osteoarthritis. The reported rate of infection has a wide range; prospective studies should be performed to determine the true rate of periprosthetic joint infection (PJI) in this subset of patients.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A study on 58,000 elective, primary total hip arthroplasties (THAs) demonstrated a deep surgical site infection (SSI) rate of 0.2% [1]. There are multiple studies reviewing the outcomes of treatment for femoral neck fractures. Most of the studies are retrospective reviews of small cohorts that are not sufficiently powered to study infection rates. Additionally, many of the studies merge primary hemi or total arthroplasty patients with patients who underwent open reduction and internal fixation, and then subsequently a secondary arthroplasty procedure. While most studies report infection rates, the primary endpoint tends to aim at a controversy in treating these fractures, such as cemented versus cementless, or performing hemiarthroplasty versus total arthroplasty. Infection rates vary from 1.2% to 4% [2–5]. A study on 90-day costs following hemiarthroplasty or THA for treatment of hip fractures demonstrated a 17.7% infection rate, but this was not limited to surgical site infections; urinary tract infections, pneumonias and other infections are included in this percentage [6]. A meta-analysis on outcomes of patients who sustained femoral neck fractures reported a 1.0% SSI rate in patients undergoing THA, 1.7% SSI rate in patients undergoing bipolar hemiarthroplasty and a 2.8% SSI rate in patients undergoing unipolar hemiarthroplasty [7].

A study from the Swedish Hip Arthroplasty compared 10,264 patients who underwent THA for treatment of a subcapital hip fracture with 76,520 patients who underwent THA for other reasons and they reported a 0.5% infection rate in the patients who were treated for fracture [8]. It appears that the rate of infection is higher in patients undergoing arthroplasty surgery for the treatment of acute femoral neck fractures.

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3.4. TREATMENT: PROCEDURE-RELATED

Author: Pedro Caba

QUESTION 1: What is the optimal timing of surgical debridement in open fractures?

RECOMMENDATION: It is not possible to establish a clear cut-off for optimal timing of open fracture surgical debridement after injury. Administration of antibiotic prophylaxis and adequacy of debridement is more important than time to debridement. However, we recommend debridement as soon as the patient and operative conditions are optimal.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Debridement is only one of the main pillars of initial open fracture treatment. Antibiotic therapy and proper fixation are also important variables. It is difficult to separate the effects of the different treatments and actions on the onset of infection and other complications. Most clinical studies demonstrate small differences in the time to debridement between comparison groups, and time cut-offs are arbitrary based on historical papers. The implementation of early antibiotic treatment in open fracture treatment has changed the infection rate. Examining the relationship between timing of surgical debridement and infection risk is crucial in guiding clinical practice, as there is still significant variability among surgeons' preferences. Most of the orthopaedic doctrine in this issue is based on historical papers or retrospective studies.

The cut-off of six hours for initial surgical debridement is based on the 1898 Friedrich study which demonstrated in an animal model that wounds debrided within six hours had no infection. This finding became incorporated into orthopaedic doctrine as the "6-hour rule." Robson supported these findings with a clinical study in 1973. He described a golden hour or inflection point of 5.17 hours after injury, which is the time needed for bacteria to reach a critical level of contamination ($> 10^5$ bacteria per gram of tissue specimen).

The first systematic review examining the relationship between infection and time to debridement was published in 2012 [1]. This review included 3,539 patients from various studies. The analyzed data did not indicate an association between delayed debridement and higher infection rates. Studies published since 2012, including a metanalysis, indicate that the 6-hour rule is not supported by evidence. Prodromidis performed a metanalysis in 2016 on the specific topic of the 6-hour rule in open tibia fractures [2]. This paper examined seven articles (only two prospective) involving 610 patients. The statistical analysis did not find any differences in terms of deep infection or non-union regarding the time to debridement.

One major limitation in this literature is the arbitrary cut-off times in the different studies. In 2014, the results of a large prospective cohort multicentre study involving 797 fractures was published. This study did not demonstrate differences in the early (< 6h), intermediate (6-12h) and late (> 12h) groups. Median time to debridement was 9h 15 min, indicating that most patients were not treated early. Another prospective study published by Srour et al. reported similar results [3]. They studied a cohort of 351 consecutive patients treated in the same facility comparing three different cut-off times (< 6 h, 6-18h and 18-24 h). They concluded that the time to operating room did not affect the development of local infectious complications, provided that the operation was performed within the first 24 hours after arrival.

Recent papers have focused on the impact of delayed debridement on infection rates, with conflicting results. Kumar et al. performed a large retrospective study of 404 patients treated with contemporary treatment. They reported that the rate of infection in open lower extremity fractures increases when debridement is delayed beyond eight hours [7]. For upper extremity injuries, delayed debridement did not result in any increase in infections. Penn-Barwell, in an experimental study on rats [8], demonstrated the timing of antibiotics had a more significant effect than surgical debridement on the onset of acute infection, especially when initation of treatment is delayed beyond six hours. When antibiotics were started at two hours, a delay in surgical treatment from two to six hours significantly increased the risk of development of infection but delays beyond six hours did not result in any increase in infection indicating that very early debridement, within two hours of the injury, could have a positive effect. Hull et al., in a prospective series of 459 patients, studied the relationship between delayed debridement and deep infection [6]. They reported that there is a 3% increased risk of infection for every hour of delay. As baseline infection risk is higher for Type IIIB and IIIC open tibia fractures than for lower grade tibia fractures, the increased risk in this group of fractures is much higher when the debridement is delayed. According to this study, the predicted probability of infection in a high grade contaminated tibia fracture increases from 35% at four hours post-injury to 45%. They recommend urgent debridement at the first reasonable opportunity after injury.

In summary, urgent debridement is essential in the initial treatment of open fractures, but the cut-off time is not known. There is little current evidence supporting the 6-hour rule. There is moderate evidence supporting the proposition that delayed debridement beyond eight hours could have an impact on infectious complications, especially in high-grade open tibia fractures. There is only limited evidence supporting very early debridement (< 2hrs).

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QUESTION 2: What is the recommended volume of irrigating fluid in the emergency department (ED) for open fractures?

RECOMMENDATION: In the ED setting, open fractures should be irrigated sufficiently to remove all visible contamination and debris prior to applying dressings.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 75%, Disagree: 15%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

Search Method: A comprehensive literature review was performed to identify all studies on the use of irrigation for the treatment of open fractures in the ED. We searched Ovid Medline, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to May 2018 for published studies. Search strategy, including keywords and MeSH headings, are provided in the Appendix. Eligible studies met the following criteria: (1) all patients included in the study had an open fracture, (2) infection was an outcome variable and (3) irrigation in the emergency setting was the intervention. Exclusion criteria were non-English language articles, nonhuman studies, retracted papers, case reports, review papers, studies without clinical follow-up/infection rates, and technique papers without patient data. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed. The initial search resulted in six papers. After removal of duplicates and screening of titles and abstracts, one article was assessed and reviewed.

RATIONALE

Thorough irrigation is a cornerstone in the treatment of open fractures. It is an important step in decreasing bacterial load and removing foreign bodies. Despite extensive literature in the management of open fractures, there has been very little data on the role of wound irrigation in the ED prior to formal debridement in the operating room. Furthermore, the literature is lacking with regard to the optimal volume of irrigation during formal debridement in the operating room [1].

One study by Basat et al. looked retrospectively at clinical outcomes of patients with open fractures of the hand treated with antibiotics and irrigation in the ED alone without formal irrigation in the operating theater. Irrigation with sterile saline was performed by the orthopaedic surgery resident, until the wound was grossly clean. The volume of irrigation and degree of wound contamination were recorded. Of the 68 open fractures treated, 14.8% developed an infection. They found that volume of irrigation correlated with development of infection, with 70.5% of fractures requiring > 1,000 ml of irrigation. They concluded that in the ED, one should use as much fluid as needed to obtain a grossly clean wound. However, this study clearly has its limitations. The degree of contamination is a highly subjective and confounding variable in the association found between increased irrigation volume and increased infection rate. This study looked at open factures of the hand, which are different from those of the lower extremity and typically have a lower degree of contamination and typically exhibit an improved ability to fight infection. Furthermore, this was a retrospective study without control or comparison groups [2].

In contrast to the ED setting, there have been several studies investigating the amount of irrigation required during formal debridement in the operating theater. However, the recommended volumes of irrigation in theater were always described arbitrarily in several published studies [3–6].

Gustilo et al. described the use of 10-14 liters of irrigation intraoperatively [4,5]. Anglen recommended the use of irrigation bags, which are readily available in three liters, for intraoperative irrigation (three liters for Gustilo type I, six liters for Gustilo type II and nine liters for Gustilo type III) without citing any supporting data [6].

Although several studies have investigated open fracture management, the volume of fluid irrigation utilized in them was based on the same rule of "3, 6 and 9" and none of them addressed the amount of irrigation used in the ED [7–11].

After review of the literature, there has been only one clinical study related to the volume of irrigation for open fractures in the ED and this was limited to open fractures in the hand and fingers. Nevertheless, in the ED setting, irrigation of the wound with enough volume until all grossly visible contamination and debris is removed seems, at the very least, an appropriate amount.

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APPENDIX - SEARCH STRATEGY

Ovid Medline: ((open adj3 fracture*).ab,ti. or "Fractures, Open".sh.) **AND** ((irrigat* or lavage or wash*).ab,ti. or "debridement".sh.) **AND**

((volume or amount or quantity).ab,ti.) **AND** ((emergen* or immediate* or urgen*).ab,ti. or "Emergency Service, Hospital".sh.) **AND** ((infection* or sepsis).ab,ti. or Infection/ or "Wound Infection".sh. or "Cross Infection".sh. or "Sepsis".sh.)

Scopus: ((open w/3 fracture*) AND (irrigat* OR lavage OR wash*) AND (volume OR amount OR quantity) AND (emergen* OR immediate* OR urgen*) AND (infection* or sepsis)) in Title, Abstract, Keywords

CENTRAL: ((open near/3 fracture*) AND (irrigat* OR lavage OR wash*) AND (volume OR amount OR quantity) AND (emergen* OR immediate* OR urgen*) AND (infection* or sepsis)) in Title, Abstract, Keywords

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QUESTION 3: What is the recommended volume and composition of irrigating fluid in the operating room for open fractures and post-traumatic wounds?

RECOMMENDATION: Irrigation in open fractures should be performed with normal saline and gravity flow irrigation. 3-9L is a reasonable volume to use. Bactericidal washes with agents like chlorhexidine or povidone-iodine have not been adequately studied in orthopaedic trauma patients, but basic science studies raise concern that they may damage tissues.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Irrigation is a central tenet in open fracture management, reducing bacterial concentrations and removing foreign materials from traumatic wounds. The goal in these injuries is to reduce the known risks of infection, wound healing problems and nonunion. Irrigation requires a balance between removing contaminants and causing further trauma to tissues or spreading contamination. Questions about irrigation include the ideal volume, fluid composition and pressure of irrigation solutions.

The one identified randomized controlled trial comparing different osmolality irrigating agents of distilled or boiled water and isotonic saline did not have clearly-defined outcome measures or follow-up criteria, but reported a 25.5% overall infection rate without any significant difference between the irrigation solutions [1].

Regarding antiseptic solutions, the majority of data is in animal or cadaveric models. This literature raises concerns about host cell toxicity that could affect wound healing or fracture union when utilizing agents such as ethanol, povidone-iodine, bacitracin solution, chlorhexidine solution, or hydrogen peroxide [2–8]. Additionally, there is some data showing that bacterial count reductions from soap or antiseptic solutions may be temporary and followed by disproportionate rebound at later time points, which has led some authors to recommend saline irrigation [9]. Regarding human clinical data, there is one moderate-quality randomized controlled study comparing bacitracin to castile soap for the irrigation of 458 open fractures in 400 patients. Minimum follow-up was 180 days, with an overall infection rate of 15.3%, a wound complication rate of 6.8% and a nonunion or delayed union rate of 23.9%. They reported similar infection and nonunion rates but increased wound-healing complications in the bacitracin group [10].

Volume

We were unable to identify any studies that specifically compared the volume of irrigation in a controlled manner in open or traumatic wounds. However, most studies used a minimum of 3L of irrigation and increased this amount by 3L per additional Gustilo type (3L for Gustilo type I, 6L for Gustilo type 2, 9L for Gustilo type 3), as in the 400-patient RCT by Anglen et al. [10].

Pressure

Pulsatile lavage theoretically improves dislodgement by cyclically compressing tissues then allowing them to decompress and recoil, freeing bacteria and foreign material. Pulsatile lavage has a proven clinical track record in reducing debris and bacterial counts in traumatic wounds when compared to gravity or bulb syringe irrigation [11–14]. However, basic science studies have raised concerns that pressurized lavage may be detrimental to bone healing and may seed bacteria distant to sites of initial contamination [5,15–18].

In the largest study on wound irrigation in open fractures, the Fluid Lavage of Open Wounds (FLOW) Group conducted an international, 41-center, blinded, randomized controlled trial assigning 2,447 patients with open extremity fractures to irrigation with high (> 20 psi), low (5-10 psi) or very low (1-2 psi) pressure with either castile soap or normal saline [19]. Irrigation for Gustilo type I injuries was 3L and types II and IIIA/B were 6L, with type IIIC injuries excluded from the trial. Of note, this study had the additional benefit of relatively standardized care in the pre-, intra- and post-op settings regarding components such as prophylactic antibiotic type and timing, skin prep solutions, debridement, skeletal stabilization and wound management including closures, dressings and soft tissue coverage. They reported no statistically significant difference between the pressure groups for the primary endpoint of reoperation within 12 months for promotion of wound or bone healing or for a wound infection. This study reported an overall 6.8% infection rate, 3.6% wound complication rate and 6.8% nonunion rate at 12 months.

The overall reoperation rate for infection, wound or bone healing was 13.2%. There was a significantly lower reoperation rate in the saline group than the castile soap group (14.8% vs. 11.6%, hazard ratio 1.32, 95% confidence interval 1.06–1.66, p = 0.01). Neither pressure nor solution composition led to significant difference in the secondary outcomes of non-operatively managed infection, wound-healing problem or bone-healing problem. In the subgroup analyses, there was a trend toward superiority without reaching statistical significance for very low-pressure irrigation in tibial fractures [19].

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QUESTION 4: What is the most appropriate management of early (prior to complete wound healing) infection after fracture fixation with stable fixation?

RECOMMENDATION: The most acceptable treatment strategy for trauma patients with early postoperative infection is to perform proper irrigation and debridement, administer intravenous (IV) followed by oral antibiotic therapy and retain stable hardware in place.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The definition and classification of early infection after isolated fracture fixation (IFF) is a dilemma among orthopaedic trauma surgeons [1–3]. However, the clinical picture of early infection including local (e.g., hematoma, wound discharge and dehiscence, erythema around the incision) and systemic (e.g., fever, lethargy) symptoms are usually diagnostic in most situations. Although it is not clear whether the biofilm formation process during the early postoperative infection period will be stopped or delayed with appropriate treatment, the goal of the treatment at this stage is to control the infection until complete union is achieved at the fracture site. After fracture healing, removal of the implant will help to eradicate the infection. This strategy is different than the typical treatment of a periprosthetic joint infection (PJI) in which the infected implant is replaced in two stages (spacer and then re-implantation of the total joint arthroplasty). The treatment strategy might be different based on the evaluation of the local and systemic clinical picture in each individual case. However, based on the available literature and our experience, it is possible to suggest some general recommendations.

The most significant difference between IFF and PJI is the higher chance of infection control and eradication by removing the implant during or after bone healing is complete for IFF cases. Therefore, especially in early postoperative IFF cases, infection control is the main goal of medical and surgical treatment [4,5]. The treatment options are described as ranging from simple antibiotic suppression to removal of the current implant to multiple stage revisions [4,5]. The most reasonable treatment strategy that is applicable to most cases is performing irrigation and debridement, retaining the stable fixation, and administering IV antibiotic therapy [4–7]. More than one washout or debridement may be necessary to clean the operative site and optimize wound healing [8,9]. Local antibiotic delivery (e.g., bead pouch, calcium sulfate beads) may be helpful. Proper soft-tissue coverage and aggressive debridement are the main principals of the surgical part of the treatment. Early flap coverage is critical if hardware is exposed [10].

The use of negative-pressure wound therapy coupled with continuous instillation of an antibiotic solution containing gentamicin and chymotrypsin has also been shown to facilitate a healthy wound bed for healing while maintaining fracture fixation with or without additional surgery for secondary closure [11]. In patients who are at high risk for wound healing problems, incisional negative-pressure therapy may be helpful following the washout [12,13].

Empiric systemic antibiotic therapy followed by organism susceptibility-based therapy should be started after early irrigation and debridement. Systemic antibiotic therapy can be curative or suppressive [14]. After a period of two weeks, IV antibiotic therapy can be replaced by appropriate oral therapy based on the available culture results [15–17]. It is recommended to continue the oral therapy for an additional four to six weeks to prevent chronic

osteomyelitis and suppress the infection [14,18]. In some situations, one may consider long-term oral suppressive therapy until union is achieved before considering implant removal.

Surgical intervention usually is needed to control the IFF. The main challenge is whether or not to remove any stable implants. Removal of stable internal fixation during the early postoperative period, especially in complex situations, will compromise bone healing. It has been shown in multiple studies that there is a strong correlation between fracture stability and bone healing [19–21]. Theoretically, proper irrigation and debridement in the early stage of the IFF can reduce the bacterial load and lower the speed of biofilm formation, which will also help the fracture consolidation process.

During initial debridement, local delivery of the antibiotic at the fracture site can be implemented by using absorbable or non-absorbable materials. However, there is no strong evidence to support the advantage of using local delivery systems as well as systemic antibiotic therapy. Aminoglycosides and vancomycin are the most commonly used antibiotics for local delivery [22]. Industrial premixed or hand-mixed polymethylmethacrylate bone cements are widely used to deliver antibiotics to the infection site by different techniques including molded beads or coated intramedullary nails [23]. The need for removal and less optimal release of the incorporated antibiotics are the main disadvantages of the antibiotic-loaded cements [24]. Good primary results are reported for resorbable materials such as calcium sulfate [25–28]. However, there is no high-quality study to show the superiority of these materials to the antibiotic -loaded cements in terms of clinical outcomes. Recently, hydrogels were introduced as an attractive and effective delivery vehicle for traumatic wounds with reasonable outcomes, which needs to be validated by further high-quality studies [22,29,30].

Although irrigation, debridement, and retention of the stable fixation device were reported as a successful treatment strategy for early IFF in a few studies, there is no strong evidence to support this treatment protocol, especially in the very early stage (before wound healing). Berkes et al. [6] reported a 71% fracture union rate in 121 patients with early postoperative (within 6 weeks) IFF after treatment with irrigation and debridement, implant retention, and culture-specific antibiotic suppression. Open fractures and the presence of an intramedullary nail were reported as the positive predictors of treatment failure. Rightmire et al. [7] reported a similar rate of bone healing (68%) with the same strategy for treatment of early IFF (within 16 weeks). However, there is no available evidence for the appropriate treatment of the infection in the postoperative period before wound healing occurs (two weeks).

Based on the available evidence and our experience, the most acceptable treatment strategy in trauma patients with early postoperative infection is proper debridement, antibiotic therapy (IV followed by oral) and retention of the stable hardware already in place.

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QUESTION 5: What is the most appropriate management of early (before complete wound healing) infection after fracture fixation with unstable fixation?

RECOMMENDATION: The most appropriate management of early (prior to complete healing) infection after fracture fixation with unstable fixation consists of surgical debridement with removal of fixation implants, fracture stabilization, antibiotic therapy and soft tissue coverage, if needed.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Infection after fracture fixation is a serious complication in orthopaedic trauma surgery, as it may eventually lead to devastating outcomes such as amputation [1]. In contrast with periprosthetic joint infections, literature regarding this condition is still limited considering the number of patients affected [1,2]. Nonetheless, in order to unify the evidence available, major efforts have been made to accurately define "infection after fracture fixation" [3]. The current definition includes a classification according to the onset of symptoms and early infection is considered that which occurs during the first two weeks after the index procedure. [2,4]. For this recommendation, this definition will be maintained.

Several systematic and non-systematic reviews gathered the existing evidence for infection associated with orthopaedic implants. All conclude that antibiotic suppression therapy and surgical debridement with implant retention is a suitable option for the treatment of early infection after fracture fixation when fracture healing has not yet been achieved, but the construct is stable [1,2,4–8]. Therefore, to date, this continues to be the standard of care for early infections. Likewise, the outcomes presented by Trebse et al. [9], Rightmire et al. [10] and Berkes et al. [11] all showed favorable results for this method of management, with success rates ranging from 68% to 92%. However, the quality of evidence of these studies is low.

The question remains whether implant retention is still a viable option for unstable fixation. Metsemakers et al. [2], in their more recent review, suggest that implant exchange or removal should be considered in early infections when intramedullary devices are used, unstable fixation exists or insufficient fracture reduction is present. These recommendations are based on the works by Trampuz et al. [4], Kleber et al. [12] and Rightmare et al. [10]. Moreover, several animal studies have addressed the importance of fracture stability in implant-related infections [13–15]. When fixation is unstable, implant retention is not an option. The existing implants do not provide enough stability at the fracture site, which will impair fracture healing as well as facilitate persistence of infection.

Even though both Rightmire et al. [16] and Berkes et al. [17] performed a multivariate analysis, neither of them reported "unstable fixation" as a predictor of treatment failure [10,11]. The quality of the presented evidence is low and the methodology used might not have been appropriate to conclude that implants must be removed under these conditions.

After performing a systematic search of the literature, no conclusive evidence on the management of early infection with unstable fixation was identified. Therefore, our recommendation is based on clinical experience, established knowledge of implant-related infection [18] and the management of infected non-unions [19,20]. Furthermore, adequate coverage of the fracture site with a well-vascularized soft tissue envelope facilitates both control of infection and fracture healing. Therefore, in the case of soft tissue defects or scarred soft tissues with poor vascularity, a soft tissue reconstructive procedure is usually necessary [21,22].

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QUESTION 6: What is the appropriate timing of conversion to internal fixation (in-fix) following external fixation (ex-fix)? How is this altered by pin site infection?

RECOMMENDATION: Timing of conversion should be based on patient characteristics including concurrent injuries and premorbid health and function, as well as injury features and location. One-stage conversion appears to have similar or even lower infection rates compared to two-stage conversion. In the absence of pin site infection, early conversion is preferred.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

American development of external fixation is credited to Parkhill in 1897 and European development to Lambotte in 1900 [1]. Ex-fix is often used in polytraumatized patients as part of a damage-control orthopaedic approach, in injuries with extensive soft tissue compromise, or when appropriate personnel or resources for in-fix are not readily available [2,3]. It is applicable to periarticular fractures, long bone fractures and articular dislocations, making it an essential component of contemporary orthopaedic traumatology.

Recent literature review using the databases Embase, Scopus, Google Scholar and PubMed was performed with the search terms "internal fixation," "external fixation," "timing" and "conversion" in multiple combinations. Articles were reviewed for relevance and studies were then assessed for quality and assigned a level of evidence.

Following ex-fix, conversion to in-fix can have multiple benefits for patients. A prospective comparison of 39 patients with open lower leg fractures treated with primary ex-fix with randomized conversion to intramedullary nailing (IMN) or to cast immobilization showed significantly shorter mean time to union (26.3 vs. 35.4 weeks), higher overall consolidation rates (94% vs. 64%), and better knee and ankle range of motion (ROM) for IMN [4]. Regarding timing of conversion from external to internal fixation (which includes plate/screw constructs and intramedullary nail constructs), major questions within the field are as follows: (1) Should conversion be performed in one procedure (acute) or in two (staged)? (2) Does time in ex-fix affect outcomes following conversion? (3) Do pin site infections increase the risk of deep infection following in-fix? (4) Does timing of soft tissue coverage affect outcomes following conversion? [2].

Regarding staging, theoretically staged conversion should allow time for pin site granulation and decrease infection rates. Therefore, some authors recommend delayed internal fixation until pin sites heal closed [5]. However, data from level IV studies do not support this. Horst et al. reported on two protocols, one for immediate conversion and one for staged conversion from external to internal fixation. They included local excision of skin-pin interfaces and curettage of soft tissues around pin track sites. For immediate conversion, pin sites were disinfected and covered prior to re-prepping of the surgical field. Pin sites were left covered until all in-fix wounds were closed, and then pin sites were left open with antibacterial dressings. For staged conversion, ex-fix was exchanged for a cast and any required soft tissue coverage was performed prior to in-fix. After institution of this algorithm utilizing the immediate conversion protocol, they observed a decrease in time to conversion (mean 6.8 > 5.0 days), hospital length of stay (mean 25.4 > 16.3 days) and complication rate (21% > 8.3%) [6].

Monni et al. performed a retrospective review of 18 patients (24 limbs) undergoing conversion from external to internal fixation for traumatic bone defects or congenital deformities. Indications for conversion included patient dissatisfaction with ex-fix, pin track sepsis, persistent non-union or refracture. In-fix consisted of IMN or plate and screw constructs. Conversion was performed acutely (19 limbs) or staged (5 limbs). The outcome was considered excellent if patients were full weightbearing, pain free, had a mechanically well-aligned limb and did not need further surgery within the follow-up period. The outcome was considered good if patients required subsequent surgery to achieve union and the outcome was considered poor if an irreversible complication occurred. The acute group had 16 excellent and 1 good outcomes (89.4%), with 2 (10.6%) poor outcomes resulting in amputation, both after acute conversion to IMN for infected tibial nonunion. The delayed group had four (80%) excellent and one (20%) good outcomes. They cautioned against using IMNs in patients with a diagnosis of an actively septic nonunion and reported that conversion to in-fix generally produces good to excellent results [7]. Bandhari et al. found that shorter intervals between ex-fix removal and IMN, for planned or salvage procedures, correlated with reduced infection, but do comment that in level IV studies this may represent confounding [8].

Farrell et al. reported on ex-fix with one-stage conversion to in-fix for nine calcaneus fractures. Ex-fix was applied within 24-48 hours and converted to open reduction and internal fixation (ORIF) through a sinus tarsi approach at an average of 4.8 days from ex-fix. There were no pin tract infections, deep infections or wound healing complications [9]. Natoli et al. reported on 16 complex distal radius fractures, 11 of which were open, and treated with an ex-fix and converted to ORIF at a mean of 8.5 days. One patient developed deep infection, and they did not report a relationship with open fractures, time to conversion of < or > 7 days, or ex-fix pins overlapping the definitive fixation [10]. Shah et al. reported on pilon and tibial plateau fractures treated with ex-fix converted to ORIF excluding cases with evidence of overt pin site infection. They demonstrated a 24% rate of deep

infection when definitive fixation overlapped pin sites, compared to 10% when it did not; a statistically significant increase [11].

Roussignol et al. performed a retrospective review of 55 patients treated with ex-fix and secondary IMN after traumatic tibial shaft fractures (16 closed, 39 open). Of note, they also excluded patients with external fixator pin site infections. They analyzed time to IMN (mean 9 +/-9.6 weeks), acute or delayed exchange (23 acute vs. 32 staged, mean 12-day interval), culture results of reaming products, post-IMN infection and time to union. There were four septic complications and one aseptic nonunion requiring re-nailing. Acute versus delayed IMN did not correlate with increased infection risk, with only open fracture grade correlating with infection risk, and the union rate was 96%. Based on these results, they therefore recommend acute (one-stage) exchange of ex-fix for IMN [12]. Bhandari et al. performed a literature review on ex-fix conversion to IMN in tibia and femur fractures, including one level II study and the remainder level IV studies. They looked at studies with planned conversion from ex-fix to IMN, and those where IMN was used to salvage failed treatment with ex-fix. In 6 studies totaling 185 patients for planned conversion for femur fracture, with a mean 10 days ex-fix and 1 day interval to IMN, the infection rate was 2.6%. For tibias, 9 studies on planned conversion (n = 268) averaged 8.6% infection and 92% union, with shorter ex-fix time (< 28 days) correlating with an 83% reduction in the risk of infection compared to > 28 days [8].

Regarding time in ex-fix, Monni et al. reported a mean ex-fix time of 185 days (range 61-370), with poor outcomes correlating with longer time [7]. Bhandari et al. performed a meta-analysis assessing when to perform conversion, with deep infection rates 83% lower when IMN was performed within 28 days compared to after 28 days [8]. These studies both suggest earlier conversion is preferable. However, Yokoyama et al. performed multivariate analysis of 42 cases of secondary IMN after open lower leg fracture treated with initial ex-fix, with 7 (16.7%) developing deep infection, and found only time to skin coverage, with a threshold of 1 week, was significantly correlated with deep infection. They did not find a relationship between infection and the duration of ex-fix (</= or > 3 weeks), the interval between ex-fix removal and IMN (</= or > 2 weeks), or the existence of superficial infection or pin tract infection [13]. Similarly, Roussignol et al. did not find a correlation between infection risk and time in ex-fix before IMN [7].

While most studies have excluded patients with active pin site infections, Yokoyama et al. did not find a relationship between superficial infection or pin tract infection and rates of deep infection after IMN [13].

Regarding timing of soft tissue coverage, the previously cited Yokoyama et al. noted restoration of soft tissue coverage within one week correlated with a decreased risk of infection [13]. Outside of external to internal fixation conversion, other literature has used the threshold of five days from initial injury to wound closure before rates of wound healing complications and infections increase [9]. Most orthopaedic literature supports earlier soft tissue coverage in open fractures as protective against infection, irrespective of fixation type [14].

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QUESTION 7: What are the alternatives to segmental resection in septic non-union?

RECOMMENDATION: Surgical alternatives to segmental resection include bone grafting, unroofing, decortication, distraction osteogenesis or intramedullary reaming to address the site of osteomyelitis. All dead bone and soft tissue should be removed.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 91%, Disagree: 0%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

Operative debridement of necrotic tissue has been a surgical principle of infection treatment for centuries. Reports from the 1960s demonstrated that it is sometimes possible to heal a fracture nonunion with bone grafting and stabilization without disruption

of the non-united bone site [1]. However, failures were common and continued infection was an expected outcome. In 1984, Cierny et al. published a classification of osteomyelitis and described both an anatomic description of the site of infection and a description of the host with recommendations for debridement strategy [2]. The fundamental principle is debridement of all dead and infected bone in the same manner that a malignancy would be treated with a marginal excision.

Cierny's guidelines are that infection involving only the medullary canal can be potentially treated with reaming or a reamer-irrigator aspirator (RIA) to achieve adequate debridement. More localized infection can be treated with unroofing or decortication of the bone segments. However, diffuse infection over a segment of the bone requires segmental resection to achieve complete debridement of all dead bone. In addition to these recommendations, segmental resection may be preferred when distraction osteogenesis is planned for the bone defect reconstruction.

Resection of the non-union followed by a two-stage procedure with the use of a spacer and bone graft/allograft, shortening, intercalary implant or bone transport after six weeks is unquestionably the gold standard of treatment [3–7]. Intravenous antibiotics are also very important in the treatment of infected non-united bone and can be used alone but functional blood supply is necessary for successful results [6,8]. A local muscle flap or pediculated bone graft with or without free flap can be used to gain infection control but these do not usually prevent infected bone resection [9–14].

In most cases, external fixation with Ilizarov´s method or unilateral fixators can be used successfully in combination with local application of antibiotic or bone-inducing agents [15–22]. Some authors describe the use of local cement application for several weeks before local bone grafting without segmental resection [23–27]. In some cases of septic non-union, the application of bone marrow with stem cells or human bone morphogenetic protein (hBMP) was used with good results [28–32]. Antibiotic-coated plates are also used in some cases [33,34]. In the ankle region specifically, arthrodesis can be an option to achieve septic union in infected cases by stabilizing the non-union site [35]and persistent drainage is only an option,albeit poor, in elderly patients [36]. It has been shown both in vitro and in vivo that cement coated implants or temporary cemented rods or spacers can be used without the need for segmental resection in septic non-union after nailing or with intramedullary infection [37–54]. There are indications where sufficient infection control for bone healing can be reached with stable implants.

Alternative strategies are the use of bioactive glass for osseous induction as an allograft or as carrier for antibiotics which showed promising results in infected bones – but blinded and randomized trials are still missing [6,55–61]. The loading of nano-particles with antibiotics, microspheres, polymer-lipids (and bacteriophages) is another very promising method, as is the induced membrane technique using beta-tricalcium phosphate [62]. The advantages of antibiotic release-control could be an important step in the treatment of infected bone non-union in the future, but Level I studies are missing here [63–81]. Furthermore, there are no comparative studies examining relative success of different debridement strategies.

Segmental resection is performed in cases of septic non-union with undersupplied, chronic infected and atrophic "dead" bone. In minor cases, segmental resection could be avoided by using other treatment options. Debridement strategies guided by Cierny's recommendations, including segmental resection when required, are recommended [82–85].

Eradication of infection is the main goal of the treatment and segmental resection can sometimes by the most useful method to accomplish this. Alternative treatments to segmental resection have not yet been determined to be as successful as the standard treatment. As of now, there is not enough evidence supporting a change of the accepted standard of care in septic non-union but some promising approaches are being explored.

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QUESTION 8: What is the optimal management (Masquelet technique, bone transport) of postinfective bone defects in different long bones (tibia, femur, humerus, etc.)? How does this vary by type of defect (conical vs. cylindrical)?

RECOMMENDATION: The type of defect (cylindrical vs. conical) was not determined to be relevant to the treatment method. Instead, optimal management of partial vs. full segmental defects is relevant. Each long bone requires different preferred methods of stabilization.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 0%, Abstain: 5% (Unanimous, Strongest Consensus)

RATIONALE

The most complete systematic review was published in 2017 by Kadhim et al. [1] This review reported that in 96 femoral segmental bone defects, monolateral external fixation with bone transport was 99.7% effective for union and 94.7% successful for function compared with 88.9% and 57.6% for circular external fixation, respectively. Supplemental internal fixation in this study decreased the external fixation time. Yin et al. [2] reported their series of 38 femoral fractures with infected segmental bone defects (average size, 6.5 cm) that were treated with application of monolateral external fixation and bone transport. The mean external fixation index was 1.5 months/cm (range, 1.3–1.7 months/cm). Only five femurs required docking site bone grafting. Good/excellent results (evaluated using the Association for the Study and Application of the Methods of Ilizarov (ASAMI) Classification) for bone were 87.3% and good/excellent results for functional outcome were 79%. Multiple other studies have reported similar results with monolateral bone transport but with fewer numbers of patients [3–5]. Docking site bone grafting is not always necessary except in longer transports that result in fibrous tissue at the docking site with some atrophy of the transported bone end [4,5]. Monolateral bone transport is much less technically challenging than classic Ilizarov transport in the femur; therefore, this technique is more accessible to a larger number of surgeons.

Few studies document the success of vascularized fibular bone grafts (VFBGs) in post-infectious segmental bone defects [6–8]. Minami et al. [6] reported on 23 post-infectious femoral segmental bone defects treated with VFBG. Twenty of 23 patients achieved primary bone union; however, 2 patients had recurrent infections. Both of these patients underwent VFBG less than one month following resection for osteomyelitis; therefore, the authors' recommendation [6] was to delay the VFBG for longer than one month after the resection and until serologic infection markers returned to normal. Gao-Hong et al. [7] reported using VFBG for infected femoral segmental defects ranging from 6 to 18 cm with primary bone healing in 10 of 12 patients. Additional surgery improved the healing rate to 100% (12/12) with eradication of infection in all cases. According to Enneking scoring, excellent/good results were observed in 11 of 12 patients [7]. Han et al. [9] reported on VFBG for defects following infection with a primary union rate of only 48%. With additional procedures, this rate increased to 77% (46/60). The literature has small numbers of VFBG reconstruction for post-infectious defects of the femur with results that are not comparable to the success of bone transport. Song et al. [10] studied post-infectious femoral defects (> 8 cm) and compared 20 cases treated with internal bone transport to 17 cases treated with VFBG. The bone transport cases had 65% excellent/good result compared to 35% in the VFBG cases. The complication rate is high regarding donor site morbidity [11] and fibular stress fractures, which range between 15% and 32% [12,13]. The VFBG technique is technically demanding, requires microsurgical skills, and is not readily accessible to many orthopaedic surgeons.

No large series has been reported of the induced membrane technique for post-infectious defects of the femur. There are 3 series with 19, [14] 13, [15] and 13 cases [16]. Wu et al. [14] reported 19 cases with an average 5.5-cm defect (range, 2–10.9 cm). The first stage was external fixation and cement spacer placement. The second stage of treatment was combined internal fixation with autograft/auto-allograft mix into the induced membrane. All femurs united and were free of infection [14]. Yu et al. [15] reported 13 cases of septic femoral bone defects averaging 9.8 cm (range, 5–16 cm). The first stage fixation was an antibiotic-coated locked plate and the second stage fixation was an intramedullary nail. The reported union rate was 100%, and 92% of patients were infection free for at least one year [15]. Tong et al. [16] also reported 13 cases of femoral posttraumatic osteomyelitis. They compared bone transport to the induced membrane (IM) technique and found that the IM technique had better results in the

femoral cases, especially the periarticular bone defects [16]. These publications [14–16] have promise but are retrospective with only small numbers.

The publications regarding the IM technique have many variations including timing to second stage, the presence of antibiotics in the spacer and the type of fixation used for stage one and two [17]. The important unifying principles are radical debridement of infection, proper installation of the cement spacer overlapping the normal bone ends, waiting for the soft-tissue envelope to heal with normal serologic markers and stable fixation during the interval prior to the second stage [18]. Infection eradication is the most essential element in achieving success. This technique therefore requires a minimum of two surgical procedures. The largest series published to date is by Karger et al. [19] with 84 cases. Fifty percent of the cases were for infection, the average number of operations to achieve union was 6.11, and 57% of the defects were larger than 5 cm. An abnormal soft-tissue envelope needs to be addressed with soft-tissue transfer (adjacent or free) in order to promote good soft-tissue healing and a stable wound bed for the second stage [20,21]. The Masquelet technique holds promise but the surgeon should proceed with caution as several surgical procedures may be needed to achieve the desired result. In theory, any size defect can be treated and there is no prolonged external fixation time as in bone transport. The time to achieve union with this technique appears to be independent of the length of the defect; however, a 2 cm defect and a 15 cm defect both may take as long as 10 months to heal [19]. The recommendation is moderate because of the lack of large prospective series reports in the literature and the number of average surgical procedures needed to achieve success.

Kadhim et al. [1] recently published a systematic review of nonunion with segmental bone defects that included 334 tibiae. The most successful method of reconstruction with respect to bone union and function was circular external fixation combined with internal fixation (either bridge plating or intramedullary nail). This provided a 99.8% success rate with respect to both union and function. Papakostidis et al. [22] also demonstrated in their systematic review that distraction osteogenesis with the Ilizarov method statistically significantly reduced the risk of infection in previously infected defects. They also showed that the risk of refracture following removal of external fixation was higher when tibial defects were larger than 8 cm [22].

Rohilla et al. [23] published a randomized prospective study with 70 patients comparing ring fixators and monolateral fixators for infected tibial defects. They concluded that for defects greater than 6 cm, a ring fixator had superior results [23]. They attributed this finding to the larger numbers of patients in the monolateral group who had residual problems with greater than 6 cm of lengthening such as infection, deformity and shortening. Also, the monolateral group had statistically significantly more problems with deep pin tract infections than the ring fixator group [23].

Many other studies have also documented the success of circular external fixation and bone transport in the tibia. Yin et al. [2] in 2014 reported 66 patients with infected segmental tibial bone defects with an average size of 6.3 cm (range, 3–13 cm). All tibiae were treated with bone transport with circular external fixation and united without recurrence of infection. Fifty-nine patients had excellent/good results according to the ASAMI classification [2]. Docking site bone graft was performed in only six patients. The most common complication was pin tract infection in 40 patients with 38 of the 40 being treated with orally-administered antibiotics and pin care. The mean external fixation index was 1.38 months/cm (range, 1.15–1.58 months/cm). Only two patients had refracture after frame removal, which was treated with reapplication of the external fixator [2]. Peng et al. [24] reported 58 cases of tibial infected nonunion with an average defect of 9.2 cm (range, 6–15 cm) that were treated with bone transport with circular external fixation. Fifty-three patients had excellent/good results using the Paley grade and 36 excellent/good functional results. There were no refractures and only one recurrent infection [24].

Hexapod external fixators have also been used for bone transport using the method of Ilzarov. Napora et al. [25] reported 75 infected segmental bone defects of the tibia (average size, 5.4 cm) treated with a hexapod external fixator. Seventy of 75 patients had eradication of infection and full union. Thirty-two patients required a free flap by plastic surgery, and 36 patients had adjunctive stabilization with either an intramedullary nail or plate fixation at or following removal. Many other articles detail the success of circular external fixation and bone transport in the tibia [26–31].

Another treatment option is acute shortening with lengthening. One paper [32] with a total of 42 patients reported similar results when comparing acute shortening with lengthening to bone transport. The only difference was a statistically significantly smaller number of major and minor complications per patient. This technique is helpful only when the fibula is broken and the soft-tissue envelope is amenable to shortening using a transverse incision. Excessive shortening greater than 4 cm can lead to ischemia of the leg due to arterial kinking and the authors highlight the need to monitor the vascular status of the limb whenever shortening is employed.

Some literature has been published on the IM or Masquelet technique for infected tibial segmental bone defects. There is some variability with respect to the technique among the papers, and some critical differences may lead to poorer outcomes using the technique. Tong et al. [16] compared the Masquelet technique for infected segmental tibial bone defects to Ilizarov bone transport. The average bone defect size was 6.8 cm (range, 2.7–15.7 cm). Twenty-six patients had tibial defects with 13 patients in each group. The IM group was treated with external fixation for stage two as well. In this series, there was no statistically significant difference between bone results in the 13 bone transport cases and 13 IM cases. It is interesting to note, however, that a recurrent infection in the IM group was treated with bone transport to union. Functional results were better in the IM group because of the statistically significantly smaller external fixation time (10.2 months [range, 8–14 months] versus 17.2 months [range, 11–24 months]). Seventeen excellent/good functional results were observed for the Masquelet technique versus nine excellent/good functional results for bone transport.

Karger et al. [19] in 2012 published the largest series of the IM technique for segmental bone defects. They included a total of 84 cases that included 61 tibial defects. Of the 61 tibial cases, there was an average time to union of 14.6 months with an average of 11.5 interventions. Full weight bearing was started at a mean of 17.4 months after the initial treatment of the bone defect. Eight tibial cases failed, and six required amputation. Qiu et al. [20] reported 40 tibial posttraumatic osteomyelitis defects. There were 2 groups: a cement bead group (18 patients) and a cement-spacer group (22 patients). The volumes of the bone defects for each group were 32.4 cm^3 (range, 15–40 cm^3) and 40.4 cm^3 (range, 20–70 cm^3), respectively. Nineteen of these bone voids were partial defects. The bone healing time was 8.5 months in the spacer group and 7.5 months in the bead group. Infection control was also similar in the two groups: 88.9% for the bead and 90.9% for the spacer groups. Eighteen patients had soft-tissue coverage by plastic surgery. Stable fixation was obtained at the initial débridement with either internal or external fixation and there were no amputations [20]. This study demonstrates that the IM technique can be successful for small defects.

Sadek et al. [33] also demonstrated that the IM technique for tibial defects smaller than 6 cm was comparable to Ilizarov bone transport in a small, case-matched series totaling 30 patients (14 and 16 patients per group). Giannoudis et al. [34] reported 43 long bones

that were treated with the IM technique; however, only 11 were tibial defects with an average defect size of 4 cm (range, 2–7.5 cm). All bones united with one complication of recurrent infection treated with repeat debridement. This study highlights one of the problems with the IM technique papers in that many different anatomic regions are considered together. Morelli et al. [35] performed a systematic review of the IM technique with 17 papers that met the inclusion criteria; however, only 10 of these papers reported individual patient data for a total of 137 cases. Persistent infection or nonunion was present in 18% of cases requiring repeat surgical interventions. There has been much enthusiasm for this technique because it is technically less challenging for the surgeon and it appeals to patients because it does not have prolonged external fixation time. This technique, however, has pitfalls with many variations of the technique being reported with variable outcomes. Surgeons should proceed with caution as recurrent infection and nonunion may require repeat operations and ultimately increase total treatment time.

Now turning attention to the upper extremity, Adani et al. [36] published a series of 13 cases of VFBG for humeral segmental defects, of which 8 were infected. The average defect in these cases was 12.3 cm (range, 10–16 cm). Five of eight patients required additional procedures (e.g., bone grafting, plate revision, new VFBG). The repeat VFBG was secondary to a vascular pedicle failure. According to Tang criteria, functional recovery was excellent/good in all eight cases and radiographically excellent/good results were seen in five of eight cases.

One series in the literature has 12 pediatric patients with humeral osteomyelitis with an average defect size of 5.5 cm [37]. Initial treatment consisted of excision of infected bone, autograft nonvascularized fibular strut and plate fixation, and limb shortening. Ten of 12 patients healed after the initial surgery. One patient required additional bone grafting. One patient developed a recurrent infection and required re-debridement and re-bone grafting with ultimate success. The average residual shortening of the limb was 3.5 cm (range, 2–6 cm).

Rafiq Barawi [37] published the results of 10 patients with infected humeral defects averaging 6 cm (range, 3–9 cm) treated with Ilizarov bone transport. All 10 cases had Paley class excellent/good results radiographically and functionally at latest follow-up, with an average external fixation index of 1.16 months/cm. Liu et al. [38] reported 11 patients with humeral osteomyelitis and segmental defects. The average gap was 1.9 cm (range, 1–2.7 cm) with an average humeral shortening of 5.6 cm (range, 3.5–8.0 cm). The average humeral lengthening was 9.5 cm (range, 5.5–13.4 cm). The average external fixation index was 1.16 months/cm (range, 1–1.35 month/cm). Ten of 11 patients healed, and all patients were eradicated of infection. All patients had excellent/good results. No docking site bone graft was performed in any of the cases. The most common complication was pin tract infection. Two pins were exchanged in two patients for loosening.

Adani et al. [39] published a series of 12 cases using VFBG in the forearm where 10 of the 12 cases had osteomyelitis. The average defect was 8.4 cm (range, 6–13 cm). Two cases required additional bone grafting and both of these cases had a history of osteomyelitis. A third case was considered a failure secondary to thrombosis of the artery of the VFBG. Therefore, 9 of 10 cases of forearm osteomyelitis healed with 2 requiring additional bone graft procedures. The average time to healing was 4.8 months (range, 2.5–8 months). Internal fixation was used for 9 of 10 cases. Seven of nine patients had excellent/good results clinically and eight of nine patients had excellent/good results radiographically.

The alternative treatment is the IM technique as applied in the forearm. Prasarn et al. [40] published a series of 15 cases of infected forearm nonunion treated with debridement and nonvascularized iliac crest bone graft with open wound healing by secondary intention. All bones united and were free of infection with an average time to union of 13.2 weeks (range, 10–15 weeks). The average defect size was 2.1 cm (range, 1–7 cm). Allende [41] in 2010 published 20 cases with healing of infection and nonunion at an average of 5 months. Luo et al. [42] published a series of 7 forearm infections with an average defect size of 5.8 cm (range, 4–8 cm) treated with the IM technique. The average number of procedures to achieve success in these patients was 3.43 (range, 2–5 procedures). The authors emphasize that a number of debridements may be required to achieve an uninfected environment. Serial debridement's were also determined by Masquelet [18] to be critical to achieve an uninfected wound bed and ultimate success with the technique. One patient required repeat bone grafting [42]. At latest follow-up averaging 86.7 months (range, 41–150 months), all patients were healed, uninfected and had statistically significant improvement in functional scores.

Two studies reported the results of bone transport in forearm nonunions. Zhang et al. [43] published a series of 16 cases with an average defect of 3.8 cm (range, 2.2–7.5 cm) with a mean external fixation index of 1.6 months/cm (range, 1.14–2.0 months/cm). All patients healed, and there was no recurrence of infection. No docking site was bone grafted. Liu et al. [44] reported on 21 patients with infected forearm nonunion who underwent treatment with monolateral fixation. The average defect was 3.1 cm (range, 1.8–4.6 cm), and the external fixation index was 1.4 months/cm. Four patients had docking site bone grafting. Three patients had regenerate bone grafting, and 3 patients had recurrent infection requiring repeat debridement. Mean follow-up was 77.5 months. All forearms healed and were free of infection.

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QUESTION 9: What is the optimum waiting time for bone grafting in staged management of septic nonunion?

RECOMMENDATION: The interval between the first and second stages should be dependent upon infection control and the status of the local soft tissue of the individual patient, rather than any specific time. Therefore, the precise time is unknown. The current recommendations are that if conditions are favorable, the second stage can be performed between 6 and 12 weeks after the first stage. This recommendation may not apply to the Masquelet technique.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Successful treatment of infected long bone nonunions remains a great challenge for the orthopaedic trauma and limb reconstruction surgeon. They are frequently associated with bone and soft tissue loss, failed internal fixation, broken implants, poor vascularity, drainage from sinuses, osteopenia, osteomyelitis, adjacent joint stiffness, deformities, length discrepancies, prior surgery and polymicrobial infection with resistant organisms [1–4]. Available evidence on the operative management of infected long bone nonunions indicates that staged reconstruction (incorporating debridement, antibiotic beads, soft tissue coverage and provisional stabilization, followed by delayed osseous reconstruction and definitive stabilization [3–6]) can achieve union in 93–100% of cases. With expert care under staged protocols by surgeons specializing in musculoskeletal sepsis, persistence of infection is present in only 2-9% of cases [5,6],

TABLE 1. Studies before 2000

Author	Year	Type of Study	Number of Patients	N Septic Nonunion	Mean Follow-up, Months (Range)	Location	Timing of Bone Grafting (Weeks)	Recurrence of Infection	Union
Green [10]	1983	Case series, retrospective	15	15	42 (24-78)	Tibia, femur, ulna	**4**	0%	87%
Esterhai [11]	1990	Case series, retrospective	42	36	Not specified	Tibia	**1**	31%	72%
Ueng [12]	1994	Case series, retrospective	13	8	37 (24-54)	Tibia	**2-4**	0%	100%
Patzakis [13]	1995	Case series, retrospective	32	32	28 (12-49)	Tibia	**8**	0%	91%
Emani [14]	1995	Case series, retrospective	37	37	24	Tibia	**2.1**	0%	100%
Cove [15]	1997	Case series, retrospective	44	12	28 (24-108)	Femur	**Min 2**	0%	92%
Chen [16]	1997	Case series, retrospective	14	14	73 (29-108)	Humerus	**6**	0%	93%
Ueng [17]	1999	Case series, retrospective	15	11	58 (40-76)	Femur	**2-6**	18%	100%

which is significantly better that one-stage strategies or two-stage strategies without local antibiotic depots using polymethyl methacrylate (PMMA) beads [2–4].

Although bone grafting is widely used for the treatment of infected nonunions, there is little evidence on the optimum timing of its use in the staged management of septic nonunion. A search in the Ovid Database (including Embase and Medline) did not identify any studies focusing on the optimum timing of bone grafting. The current evidence is based on studies that report outcomes on the management of infected nonunions. The most commonly reported prerequisite for bone grafting is complete eradication of infection. This is confirmed either clinically (absence of systemic signs such as fever or local signs such as dry healed wounds), by laboratory tests (normalization of inflammatory markers) [7,8] or by biopsies [9].

There has been only one randomized control study on the management of infected nonunion [8]. This study compared the use of antibiotic-impregnated autologous cancellous bone graft with pure autologous cancellous bone graft in the management of infected nonunions. The timing of bone grafting depended on whether muscle transfer was required. Bone grafting was performed after five weeks on average (range two to seven weeks) from the last debridement and application of PMMA if muscle transfer was not required and on an average 10 weeks (range 8 to 12 weeks) if muscle transfer was required. There were no results reported specifically for the two groups with different timing of bone grafting. This study showed that antibiotic-impregnated bone graft was associated with lower rates of recurrent infections than pure bone graft. The rest of the published studies were case-series reporting outcomes on the staged management of infected nonunions.

Interestingly, there has been a change in the timing of bone grafting for the staged management of infected nonunions over the course of the past several decades. Prior to 2000, the mean time of bone grafting was four weeks following the first-stage procedure [10–17] (Table 1). Furthermore, in only two [13,16] out of the eight published studies, bone grafting was carried out later than four weeks from the first-stage procedure. On the contrary, after 2000 the mean time between the first and second stages was 7.9 weeks and in no study was bone graft implanted earlier than four weeks from the first stage [7–9,18–35] (Table 2). This could be partially explained by increasing popularity of the induced membrane technique. The most recent case series use the principles of this technique for the effective eradication of infection and reconstruction of bone defects. The time interval between the two stages of the procedure is essential not only for the eradication of the infection but also for the maturation of the induced membrane. This may be another reason towards the shift of longer waiting times between the two stages.

In summary, even though there are no studies assessing the optimum timing of bone grafting in the management of septic nonunion, current case series recommend an interval of 7-8 weeks while most studies range between 6-12 weeks following debridement.

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TABLE 2. Studies after 2000

Author	Year	Type of Study	Number of Patients	N Septic Nonunion	Follow-up	Location	Timing of Bone Grafting (Weeks)	Recurrence of Infection	Union
Chan [8]	2000	Randomized, prospective	96	96	57 (48-72)	Tibia	**5 or 10**	11%	99%
Tulner [18]	2004	Case series, retrospective	47	22	94 (24-163)	Tibia	**4-7**	18%	95%
Chen [19]	2005	Case series, retrospective	18	18	48 (24-74)	Tibia	**6 or 11**	0%	72%
Jain [20]	2005	Case series, retrospective	42	18	Not specified	Femur, tibia, humerus, forearm	**6**	6%	100%
Babhulkar [21]	2005	Case series, retrospective	113	14	40 (24-180)	Tibia, femur, humerus, forearm	**6-8**	0%	100%
Schöttle [22]	2005	Case series, retrospective	6	6	36 (18-60)	Tibia	**15**	0%	83%
Chiang [23]	2006	Case series, retrospective	12	7	31 (24-37)	Tibia	**Min 13.5**	14%	86%
Ryzewicz [36]	2009	Comparative, retrospective	44	14	Not specified	Tibia	**6**	21%	93%
Stafford [24]	2010	Case series, retrospective	27	7	12	Tibia, femur	**6-8**	14%	57%
Allende [7]	2010	Comparative, retrospective	20	13	18 (10-96)	umerus, forearm	**8.5**	0%	100%
Schröter [25]	2015	Case series, retrospective	18	18	70 (24-96)	Femur	**Min 6**	0%	83%
Scholz [26]	2015	Case series, retrospective	13	13	13 (9-24)	Tibia, femur, fibula, radius, metatarsal	**9.8**	0%	100%
Olesen [27]	2015	Case series, retrospective	8	2	Min 9	Tibia, femur	**7**	0%	50%
El-Alfy [28]	2015	Case series, prospective	17	12	23 (14-38)	Tibia, femur	**11.3**	8%	92%
Mauffrey [9]	2016	Case series, retrospective	12	12	14-23	Tibia	**6-8**	0%	unknown
Canavese [29]	2016	Case series, retrospective	5	4	39 (24-60)	Femur, humerus	**4**	0%	100%
Davis [30]	2016	Case series, retrospective	9	7	42 (18-137)	Forearm	**6-12**	0%	100%
Giannoudis [31]	2016	Case series, retrospective	43	21	Min 12	Tibia, femur, humerus, metatarsal, forearm	**6-8**	5%	95%
Pollon [32]	2016	Case series, retrospective	16	3	78 (12-160)	Humerus	**8.6**	0%	67%
Gupta [33]	2016	Case series, retrospective	9	8	21.5	Tibia	**4-6**	25%	75%
Wang [34]	2016	Case series, retrospective	32	32	27 (24-32)	Tibia, femur	**8.9**	0%	100%
Mühlhäusser [35]	2017	Case series, retrospective	8	3	Min 12	Tibia	**8.7**	0%	100%

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3.5. TREATMENT: MANAGEMENT OF HARDWARE

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QUESTION 1: When should hardware be removed when treating surgical site infection (SSI) in orthopaedic trauma?

RECOMMENDATION: The decision to retain or remove hardware differs by clinical scenario and must take into account extent of the infection and stability of the hardware and fracture.

A methodical approach that addresses the pathogen, host factors and bony and soft tissue deficiencies is required, and includes thorough debridement, dead-space management and soft tissue and bony reconstruction using the established principles of the reconstruction ladder.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 0%, Abstain: 5% (Unanimous, Strongest Consensus)

RATIONALE

Acute or Subacute Infection with Stable Hardware and Fixation

When dealing with orthopaedic implant-related infections, the most common recommendation of nonsurgical consultants is to remove all hardware, obtain deep cultures and administer antibiotics. This is unfortunately only partially correct. Cultures are helpful, and antibiotics are essential, but the removal of stable, functioning hardware in the setting of an acutely infected fracture

should generally be resisted. Although it is well-known that the presence of inanimate material surfaces increases the risk of infection, lowers the inoculum necessary to cause infection and reduces the chances of successful treatment, longstanding clinical experience has demonstrated that skeletal stability reduces the infection rate [2,3]. This reduction is supported by the results of animal studies [4,5]. The mechanism by which instability promotes infection is not clear, but may have to do with interference with revascularization of injured tissues, ongoing tissue damage, altered fluid-flow behavior locally or increased micro-dead space. Although instability seems to interfere with the resolution of infection, the presence of infection does not necessarily prohibit bone healing. A logical strategy is to maintain stable internal fixation, which will facilitate union, and plan for hardware removal later if infection persists after the bone is healed.

For the treatment of acutely infected fractures, Berkes et al. reported a 72% rate of fracture union and resolution of infection utilizing a standardized protocol of operative debridement, retention of *stable* fracture hardware and culture-specific intravenous antibiotics. Factors that were predictors of treatment failure included the injury being an open fracture ($p = 0.03$), the presence of an intramedullary nail ($p = 0.01$), a high association with smoking and any infection with Pseudomonas species or other gram-negative organisms [6].

Other authors have also identified factors that contribute to the successful salvage of acutely infected fractures. These include the maintenance of stable hardware and time of surgery to infection diagnosis less than two weeks [7].

Another factor for successful salvage is the ability to achieve a thorough debridement of the fracture construct. If a collection of pus exists around an implant or under a flap or incision, it must be thoroughly drained. Incisions made for irrigation and debridement of infection should rarely be closed and should be placed carefully to avoid exposing hardware, bone, tendon or neurovascular structures. If these are unavoidably exposed, consideration should be given to flap coverage of the wound. The ability to achieve competent wound closure is another predictor of successful salvage. Vacuum-assisted closure (VAC, (Kinetic Concepts, Inc.)) dressing can be used temporarily in the short-term while awaiting definitive coverage.

As mentioned previously, culture specific antibiotic treatment should be standard when treating acutely infected stably fixed fractures. Furthermore, consideration to adding rifampin to culture proven Staphylococcal infections should be strongly considered. A randomized controlled trial to evaluate the utility of adding rifampin to Staphylococcal infection associated with stable orthopaedic implants demonstrated a 100% cure rate in the group treated with ciprofloxacin-rifampin compared to the 58% cure rate in the group receiving ciprofloxacin-placebo [8]. All patients underwent an initial debridement followed by a two-week course of an intravenous antibiotic regimen of flucloxacillin or vancomycin with rifampin or placebo. Long-term therapy was either ciprofloxacin-rifampin or ciprofloxacin-placebo.

In a study by Rightmire, et al. [9] outcomes in patients with acute infections after fracture repair managed with retained hardware were reviewed. They evaluated the effectiveness of irrigation, debridement and antibiotic suppression in the setting of retained hardware. A successful outcome was defined as a patient obtaining fracture union with the original hardware in place. A failure was defined as a patient requiring hardware removal before fracture union [9]. There was only 68% success with an average of 120 days until fracture healing, and 36% of these patients went on to present with reinfection. The majority of the infected fractures that failed debridement and antibiotics with retained hardware failed within three months.

It is important to consider all information when deciding to retain or remove hardware in treatment of these infections, including the specific characteristics of the fracture, the type of fixation, the virulence of the pathogen and physiology and function of the patient.

Acute or Subacute Infection with Unstable Fracture, Fixation and/or Hardware

The presence of excessive motion, the displacement of hardware on radiographs or the visualization of radiolucencies around screws, rods or fixator pins denotes an unstable situation. This instability compromises the ability to overcome infection and to heal the fracture. Bacteria that are attached to surfaces such as metallic fixation devices or dead bone become resistant to the action of antibiotics through the production of biofilm. In the face of unstable hardware or fracture malalignment, the hardware should be removed.

Animal studies with an infected fracture model document the detrimental effects of fracture instability. The infection rates at two weeks post-infection were lower in internally-fixed fractures with stable fixation compared to unstable fractures with loose pins. Stability lowers the incidence of *S. aureus* infection and other gram-positive organisms. However, gram-negative infections were less likely to be successfully suppressed in the internally fixed group and the infection could only be eradicated if the hardware was removed [5].

Friedrich et al. noted similar findings in infected fractures with retained hardware [4] and infection developed in 45% of unstable fractures. However, infection did NOT occur after rigid fixation. With rigid fixation, no significant difference in the time to bony union was noted between the infected versus uninfected fractures. It is important to note that fracture instability, particularly with loss of fixation, may also be a confounded clinical scenario, demonstrating a more widespread infection that prevents callus formation and leads to bone loss and loss of fixation.

Chronic Osteomyelitis

Debridement

Chronic infection after injury is largely a surgical disease and is rarely successfully treated by antibiotics alone. Surgical debridement should be undertaken by experienced surgeons using particular techniques that adhere to established principles, many originally described by Cierny [10–14]. If infection persists after fracture union, hardware must be removed and avascular bone and soft tissue debrided. In general, previous incisions should be used, and all necrotic soft tissue should be removed [10–14]. In the case of structures important to function and with questionable viability (tendons and ligaments), a staged approach can be taken. Care should be taken to not strip viable periosteum from bone. Sclerotic or sequestered bone should be removed until all the remaining bone appears healthy and bleeds well. A high-speed burr is a gentle way to accomplish removal of necrotic infected bone [10–14].

Local Antibiotic Delivery

To prepare defects for grafting or coverage following debridement, antibiotic-impregnated polymethyl methacrylate (PMMA) beads, rods or blocks are often placed to deliver a high concentration of antibiotics locally while avoiding systemic toxicity. Antibiotic elutes from the PMMA by diffusion from the surface. Although most of the drug elutes in the first 24 hours, therapeutic levels of drugs have been detected in some cases for as long as 90 days. Tissue concentrations may be higher and persist longer than those seen in

elution experiments. Although many surgeons believe that antibiotic beads used to treat osteomyelitis should be removed, one retrospective study suggested that improved outcomes followed leaving the beads in situ [14].

After removal of an intramedullary rod, placement of antibiotic beads offers no mechanical support. Beads within the intramedullary canal must be removed within 10 to 14 days or subsequent removal may be extremely difficult [15,16]. Antibiotic cement rods can be custom-made at the time of surgery using varying chest tubes as molds [16]. Following thorough medullary canal debridement, the antibiotic rod is inserted and does provide some mechanical stability**.** If additional debridements are necessary, the antibiotic rod is exchanged. At the time of definitive closure, the antibiotic rod is left intact in the canal, and the wound is closed directly over it. After a six- to eight-week interval, the rod can be removed and bony reconstruction can be undertaken.

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QUESTION 2: Which surgical treatment (plate, nail or external fixator) for open tibial shaft fractures results in lower rate of infection?

RECOMMENDATION: There is little to no difference in terms of infection rates for Gustilo-Anderson types I–II treated by either circular external fixator, unreamed intramedullary nail or reamed intramedullary nail. For Gustilo-Anderson IIIA-B fractures, circular external fixation appears to provide the lowest infection rates when compared to all other fixation methods.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

A systematic review was undertaken on all English language articles on infection rates following the treatment of open tibial shaft fractures. The literature search included Google Scholar and the Medline, Embase and Cochrane databases. The search terms included open tibia, tibia fracture and tibial diaphysis with the Boolean terms 'AND' and 'OR.' All abstracts were reviewed, and the full articles were obtained for all potentially suitable articles.

Review articles and those that included peri-articular open fractures and pediatric fractures were excluded. A total of 54 articles were excluded for review. Information regarding Gustilo-Anderson types and infection rates were extracted from all included articles (Table 1).

Statistical analysis revealed that across all Gustilo-Anderson types, circular external fixation and intramedullary nailing have significantly lower infection rates compared to plate fixation or monolateral external fixation. Across all types, there is minimal to no difference between circular external fixation and unreamed intramedullary nailing or reamed intramedullary nailing (Table 2).

When Gustilo-Anderson type IIIB injuries are isolated, circular external fixation appears to have a significantly lower risk of risk of infection when compared to reamed and undreamed intramedullary nail fixation (Table 4).

In conclusion, from the available published English literature on infections rates for open tibial shaft fractures treated by various different fixation methods, plate fixation and monolateral external fixation have significantly higher infection rates when compared to circular external fixation or intramedullary nailing. There appears to be little to no difference for Gustilo-Anderson types I – IIIA treated by either circular external fixator, unreamed intramedullary nail or reamed intramedullary nail. For Gustilo-Anderson type IIIB fractures, circular external fixation appears to provide the lowest infection rates when compared to all other fixation methods.

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TABLE 1. Summary of infection rates with different fixation methods from the literature review

Fixation	Type	Cases (n)	Infected Cases (n)	%
Plate [1–4]	GA I	49	3	6.1
	GA II	80	7	8.8
	GA IIIA	36	9	25.0
	GA IIIB	34	5	14.7
Monolateral external fixation [1,3–19]	GA I	9	0	0.0
	GA II	76	2	2.6
	GA IIIA	373	41	11.0
	GA IIIB	238	50	21.0
Circular external fixation [17,18,20–28]	GA I	10	0	0.0
	GA II	63	0	0.0
	GA IIIA	145	3	2.1
	GA IIIB	198	6	3.0
Unreamed Nail [1,4,5,7,9–13,16,19,29–51]	GA I	533	6	1.1
	GA II	734	19	2.6
	GA IIIA	554	32	5.8
	GA IIIB	558	102	18.3
Reamed Nail [6,18,21,32,33,38,40,41,48,52–54]	GA I	401	6	1.5
	GA II	493	15	3.0
	GA IIIA	230	5	2.2
	GA IIIB	240	40	16.7

TABLE 2. Infection rate ratio (IRR) differences between all treatment types for all GA types (I, II, IIIA and IIIB)

Treatment	IRR	95% CI	p-value
Circular fixator	Reference		
Plate	5.57	2.73 - 11.38	<0.001
Monolateral fixator	6.17	3.12 - 12.23	<0.001
Unreamed nail	3.10	1.03 - 9.25	0.044
Reamed nail	2.24	0.73 - 6.89	0.161

TABLE 3. Infection rate ratio (IRR) differences between all treatment types for GA types I, II and IIIA

Treatment	IRR	95% CI	p-value
Circular fixator	Reference		
Plate	8.34	2.78 – 25.23	<0.001
Monolateral fixator	6.82	2.57 – 18.12	<0.001
Unreamed nail	2.27	0.74 – 6.96	0.044
Reamed nail	1.68	0.63 – 4.47	0.161

TABLE 4. Chi squared analyses of infection rates of reamed and unreamed nail vs. circular fixators for Type IIIB open fractures

Treatment	OR	95% CI	p-value
Circular fixator	Reference		
Unreamed nail	6.40	2.65 – 15.44	<0.001
Reamed nail	7.19	3.09 – 16.59	<0.001

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QUESTION 3: When performing intramedullary (IM) fixation, what is the evidence regarding reaming versus non-reaming and the association with infection?

RECOMMENDATION: Based on the current evidence, there is no difference in infection rates following IM fixation of long bone fractures using a reamed or non-reamed technique.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Using an IM fixation technique has become the accepted standard in treating long bone fractures. Tibial fractures are the most common type of long bone fracture encountered and therefore are the most studied in the current literature [1,2]. Evidence has supported that IM nailing is superior to external fixation with regards to patient outcomes [3–5]; however, there has not been a consensus with regard to reamed versus non-reamed IM nailing technique.

Classically, the arguments against the use of reaming point to the risk of fat embolization from the marrow-generated from the increased intramedullary pressure created during the technique, and development of acute respiratory distress syndrome (ARDS) [6,7]. Also, long bone fractures are often the result of high-energy injuries and are accompanied with varying degrees of periosteal stripping [4]. This inherent soft tissue damage can predispose patients to complications, such as infections, especially in open fractures. In addition to the soft tissue compromise secondary to the trauma, reaming has also been shown to disrupt endosteal blood flow and to cause thermal necrosis of the bone [4,7]. This is thought to have the potential to further increase the risk of infection due to added insult to the soft tissue [4]. To avoid such adverse effects and complications, a non-reamed IM nailing technique was developed.

Despite the described adverse results of reaming, current literature has not convincingly proven an association between reaming and infection rates. Finkemeier et al. conducted a prospective, randomized study analyzing 94 patients with closed and open tibial fractures treated with either reamed or non-reamed IM nailing [8]. There was no statistically significant difference in the infection rate between the two study groups. When comparing infection rates of only closed fractures treated with reamed and non-reamed techniques (4% vs. 4%, p = 0.945), no statistical difference was observed [8]. Open fractures also had no significant difference in infection rates when treated with the studied techniques (5% reamed vs. 4% non-reamed, p = 0.851) [8]. Similarly, Blachut et al. conducted a prospective study of 141 fractures randomized into reamed and non-reamed groups and found no increased rate of infection [9]. Both of these studies noted that their smaller sample sizes could limit the quality of the evidence they presented [8,9].

A much larger prospective, blinded randomized trial was conducted by the Study to Prospectively Evaluate Reamed Intramedullary Nails in Patients with Tibial Fractures (SPRINT) investigators [1]. This study randomized 1,319 tibial shaft fractures into reamed or non-reamed cohorts and did not allow re-operations for nonunion to occur before six months in order to effectively evaluate the outcomes of the techniques [1]. The results of their study found a statistical difference in the relative risk (RR) of a primary event when a reamed technique was used in a closed tibial fracture (RR = 0.67 confidence interval (CI), 0.47-0.96, p = 0.03) [1]. The RR of an infection in a closed fracture, however was not statistically significant when comparing the reamed and unreamed groups (RR = 1.37, CI 0.48-3.93, p = 0.56) [1]. The same was seen in open fractures when comparing the infection rates of the two techniques (RR = 1.27, CI 0.67-2.40, p = 0.46) [1]. The SPRINT trial was unable to draw any conclusions about risks of infections between reamed and non-reamed techniques due to disparity between the study groups. The authors of the study noted that there was potential bias in their study, for their surgeons had more expertise with the reamed technique [1]. This could have biased their data against the non-reamed group.

A systematic review and meta-analysis of a pooled group of 646 patients conducted by Bhandari et al. found a RR of reamed versus nonreamed IM nails of 0.98 (CI 0.21-4.76, p = 0.86) for rate of infection [10]. They did note trends in favor of reamed IM nailing with closed fractures and nonreamed IM nails in open fractures. Due to the lack of significance in the results, however, they were unable to draw definitive conclusions pertaining to infection rates between the studied techniques [10]. Foote et al. conducted a network meta-analysis to analyze all treatment options for open tibial shaft fractures [2]. Similar to Bhandari et al., they were unable to find a difference between reamed and non-reamed IM techniques (direct evidence non-reamed vs. reamed odds ratio (OR) = 0.74, CI 0.45-1.24) [2].

A third systematic review was also unable to establish a statistically significant difference between infection rates when using a reamed technique as opposed to a non-reamed technique (RR = 1.19, CI 0.71-2.00) of the 1,545 patients included in this analysis [11]. Of note, the Duan et al. systematic review was heavily dominated by the inclusion of the SPRINT trial which contributed the majority of the patients to the overall analysis and was cited as a potential weakness of their study [11].

Despite concern of an increased rate of infection when a reamed technique is used for IM nailing, current evidence has been unable to elucidate a difference between reamed and non-reamed IM nails in this regard. There are several studies addressing the issue, however smaller sample sizes in all of these studies prevents one from drawing a definitive conclusion [8,9,11]. In addition, the current literature focuses primarily on outcomes aside from infection. The high-energy nature of fractures treated with these techniques as well as the open/closed nature of the injury can also be confounding factors limiting many authors' ability to draw definitive conclusions. Therefore, there is no conclusive evidence linking

IM reaming with increased rates of infection when compared to non-reamed techniques.

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QUESTION 4: Are antibiotic coated rods (ACRs) and antibiotic coated plates (ACPs) an acceptable alternative to cement only implants?

RECOMMENDATION: Antibiotic-loaded polymethyl methacrylate (AL-PMMA) spacers can be considered an established treatment concept for local antibiotic delivery in osteomyelitis and implant-associated infections.

ACRs and ACPs can also be of value in specific indications, mainly infected non-unions, in order to address both local delivery of antibiotics and biomechanically stable fixation of the non-union site to allow for possible spontaneous bone consolidation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 91%, Disagree: 5%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Biomechanically stable ACRs, such as antibiotic coated interlocking nails, and ACPs exhibit the advantage of additionally providing sufficient biomechanical stability to allow for bone healing in infected non-unions compared to antibiotic delivery only by biomechanically unstable drug carriers. There are only a few limited case series available on biomechanically stable ACRs [1–4] and ACPs with the study of Conway et al. being the largest with 110 patients on locked ACRs that were retrospectively analyzed [1]. A good overall clinical outcome could be accomplished with an overall limb salvage rate of 95% (105/110 patients) in infected non-union and infected arthrodesis.

For ACPs, there is only one case report and one case series with four patients all of whom showed healing of the formerly infected fracture by the use of the ACPs [5,6].

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QUESTION 5: What is the ideal composition of antibiotic-impregnated intramedullary (IM) nails?

RECOMMENDATION: The ideal composition of antibiotic-impregnated IM nails is unknown. The core should consist of a rigid structure such as an Ender's IM nail, Ilizarov threaded rods, IM locked nails, carbon fiber nails or sectioned pins or guidewires. We recommend at least 2 grams of vancomycin and 2.4 grams of an aminoglycoside be added to each pack (40 grams) of polymethyl methacrylate cement. If a specific micro-organism is isolated, targeted antibiotic therapy should be included.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 86%, Disagree: 9%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Infection following IM nailing of long bone fractures is a recognized complication that can be difficult to treat successfully [1]. The incidence is variable depending on the degree of soft tissue and bone compromise, ranging from 1.8% in closed fractures and Gustilo type I open fractures up to 12.5% in type IIIb open fractures [2]. Almost half of these are caused by multiple organisms. Zych et al. [2] reported that 56% of these infections were caused by a single organism, predominantly caused by *Staphylococcus aureus* (50%) followed by *Bacteroides fragilis* (3%) and *Streptococcus pyogenes* (3%). The remaining cases were caused by a combination of these and *Enterobacter cloacae, Serratia marcescens, Proteus mirabilis, Escherichia coli,* and *Pseudomona aeruginosa*. In all infections, *Staphylococcus aureus* was present in 64% of cases.

Antibiotic cement-impregnated IM nails (ACIMNs) have been described as a treatment option for this complication. These are designed to provide stability while delivering local antibiotics. Initially described by Paley and Herzenberg in nine cases, they used a chest tube as a mold and a guidewire as a core, covered with antibiotic-loaded bone cement [3]. The treatment strategy with the use of ACIMNs is generally performed in a two-stage fashion. An initial debridement and implantation is followed by subsequent removal with or without definitive hardware exchange [4–6].

The greatest disparity among ACIMNs is the element used as the core. Investigators have reported different components including Ender's IM nails, Ilizarov threaded rods, IM locked nails, interlocked carbon fiber nails, sectioned pins or guidewires [7]. ACIMNs act as antibiotic-loaded cement spacers, similar to those used in two-stage exchange arthroplasty for periprosthetic joint infection treatment, [8] with additional temporary fracture or bone stabilization [9].

Regarding construct rigidity, the core diameter is the most important factor. It is important to note that these are significantly weaker than conventional IM nails given the antibiotic coating. Thus, a balance between the core diameter and planned diameter of ACIMN should be carefully calculated. In a mechanical study by Marmor et al. [10] different core diameters were evaluated. A 5.8-mm-core diameter cement rod bending stiffness was reportedly higher, 4.96 ± 0.67 N/m2, than a 3-mm-core, 3.07 ± 0.28 N/m2, ($p = 0.0039$). The second important factor is the thickness of the cement mantle, which is currently unknown given different variables of the cement composition. Vaishya et al. [11] suggest a cement mantle thickness of 2 to 3 mm without clear evidence supporting this statement. The reduction in the volume of cement coating raises concerns regarding the effectiveness of antibiotic delivery. However, the elution properties of the impregnated antibiotics have been shown to depend on the surface area and porosity of the mixture, not the thickness. In a study by Karek et al. [12], they demonstrated that a thin mantle would potentially allow for higher elution of antibiotics caused possibly by the result of a cooler exothermic reaction.

Different techniques of ACIMN fabrication have been described [3,7,13]. The use of a mold and manual fabrication has been commonplace for the past two decades. These have different advantages and disadvantages such as fabrication speed and the morphology of the implant. Molds such as chest tubes seem to be the best option as they generate a smooth implant that facilitates their later removal. Kim et al. [5] evaluated the time required to peel the chest tube off the ACIIN using different cement-cooling techniques. They found that the fastest and most effective way is cooling the cement in cold water and pre-lubricating the chest tube with mineral oil. They also recommend the use of 3-mm beaded IM guidewire that is cut to a length 3 cm longer than the length of the tube allowing creation of a hook or loop for subsequent removal.

Broad-spectrum antibiotics are routinely used as infections are generally poly-microbial. The most commonly used antibiotics are vancomycin, tobramycin, gentamycin or a mixture of these [14]. Antibiotics must have certain properties in order not to compromise their efficacy. Anagnostakos et al. [15] identified these properties as availability in powder form, wide spectrum coverage, bactericidal activity, high elution properties, thermo-stable and hypoallergenic [16]. Targeted therapy if a micro-organism has been isolated is desired if certain criteria are met.

Reported success rates range with the use of ACIMNs range from 69% to 100% with the use of different constructs and similar antibiotic compositions [4,6,17–21]. We, therefore, consider the ideal composition currently unknown. We do consider, with the available literature descriptions, that there are several considerations that need to be employed in the construction of these devices. The core should consist of a rigid structure with the largest diameter possible to increase rigidity while not compromising cement mantle stability. The system should have an extraction element for subsequent removal. Based on recommended antibiotic concentrations for spacers, most authors use a mixture of at least 2 gm of vancomycin and 2.4 gm of an aminoglycoside in 40 gm of bone cement. Prior research has shown that this is the minimum concentration needed for attaining long-lasting antibiotic elution in the surrounding space [22]. There is little evidence of systemic toxicity with high antibiotic concentrations in the cement mixture used to coat nails, but a dosage safety range has not been established. If a specific micro-organism is isolated, targeted antibiotic therapy should also be considered.

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QUESTION 6: What is the ideal composition of antibiotic impregnated (ABI) spacers/beads in post-traumatic infections? Is preoperative microbial identification necessary?

RECOMMENDATION: There is currently limited evidence with regards to the ideal composition of ABI polymethyl methacrylate (PMMA) spacers or beads in post-traumatic infections and the need for preoperative identification of the causative organism. Available data suggests that PMMA spacers, empirically impregnated with at least 2 gm of vancomycin per 40 mg of PMMA (with or without gentamycin), may result in quiescence of infection in a high percentage of cases with an acceptable associated rate of bony union. Preoperative microbial identification is of unclear utility.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 95%, Disagree: 0%, Abstain: 5% (Unanimous, Strongest Consensus)

RATIONALE

The challenge of achieving adequate local tissue antibiotic concentrations with systemic antibiotics has prompted the addition of local antibiotic therapy in the majority of bone infection protocols. The use of ABI PMMA beads is well established in the treatment of chronic osteomyelitis. Klemm reported a cure rate of over 90% in 405 cases of chronic sequestrating osteomyelitis with the use of gentamycin-impregnated PMMA bead chains [1]. Notably, the beads were pre-manufactured with gentamycin and Klemm found no change in the gentamycin resistance profile over a seven-year period. The use of local antibiotic therapy has also been advocated in the post-traumatic setting. Numerous review articles advocate for the use of ABI PMMA or other forms of local adjuvant antibiotic therapy in the setting of septic non-union or post-traumatic infections [2–5]. Interestingly a recent comparison of the outcomes of treatment with ABI beads versus spacers revealed no difference in the rate of infection control, time to union or complication rate with either configuration [6].

The induced membrane ("Masquelet") technique has gained popularity in the management of post-infective bone defects [7]. The procedure involves the placement of a PMMA spacer in the defect, followed by a subsequent second-stage bone grafting into the resulting induced membrane [8]. Originally the procedure was described using bone cement without antibiotics. Masquelet reasoned that the inclusion of antibiotics may increase the risk of resistance to the offending organisms and that it changed the biological characteristics of the induced membrane [9]. This concern was validated, in an animal model by Nau et al., who demonstrated variations in the nature of the induced membrane with different types of bone cement and supplemental antibiotics [10]. Notably, Palacos[å] with gentamycin still resulted in a positive rate in cell growth. However, in clinical studies involving post-traumatic (not post-infective) bone defects the concerns regarding inhibition of bone healing were not realized, with reported union rates of 82% (in cylindrical defects) to 100% (in conical defects) with the use of ABI spacers [11,12].

While the original technique involved PMMA without antibiotics, several other authors have utilized the potential advantage of local antibiotic elution during the construction of the spacer [13–18]. If the data from the meta-analysis by Morelli et al. is scrutinized it appears that there may well be a therapeutic advantage with the addition of antibiotics in terms of infection control. When evalu-

ating the studies that included only post-infective bone defects it is noteworthy that there was recurrence of infection in two out of 17 cases in which PMMA without antibiotics was used, [19] compared to no recurrence in 58 cases in which ABI spacers were used [5–8]. Furthermore, the addition of antibiotics may not necessarily result in inferior bony healing with union reported in 100% of the cases in which ABI PMMA spacers were used. The heterogeneity of these studies, however, prevents drawing firm conclusions in this regard. The successful use of ABI spacers has, however, recently been corroborated in a larger series (involving 22 cases of acute post-traumatic defects and 21 post-infective defects) by Giannoudis et al., who reported an overall union rate of 93% and only one case of recurrent infection at 2-years follow-up.

Despite the promising results that have been achieved with ABI PMMA, the optimal composition of the spacers remains to be determined. Rathbone et al. examined the effect of 21 different antibiotics on the viability and osteogenic activity of osteoblasts. Amikacin, tobramycin and vancomycin were found to be the least cytotoxic agents [20]. No well-designed comparative clinical studies to asses different spacer compositions have yet been performed in the post-infective setting. The choice of antibiotic appears to be empirical in most studies and none have reported it is necessary to preoperatively determine the causative organism. The most popular composition appears to be 2 to 4 gm of vancomycin added to 40 gm of PMMA with or without gentamycin (or tobramycin) [5,6,10–12].

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Author: Volker Alt

QUESTION 7: Should antibiotic cement rods (ACRs) be left permanently in situ?

RECOMMENDATION: If the ACR is used as a temporary non-locked implant for infection control, it should be removed and replaced by a biomechanically stable construct (e.g., locked intramedullary nail). If the ACR is used as a locked implant for both local delivery of antibiotics and provision of stable biomechanical conditions for consolidation of the non-union site, it can be left in place.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 70%, Disagree: 30%, Abstain: 0% (Super Majority, Weak Consensus)

RATIONALE

ACRs can be used for two different indications.

1. ACRs are used as non-locked temporary implants for the local delivery of antibiotics into the intramedullary canal to eradicate the infection. In cases with stable bone conditions, e.g., chronic osteomyelitis in long bones, missing rotational stability of the ACR is not relevant, whereas in infected non-unions with unstable bone conditions, the ACR is removed after infection control and replaced by a biomechanically stable implant, in most cases by a standard interlocking nail in a subsequent revision procedure.

For this indication, only technical notes, case reports and small case series with a maximum of 19 cases in one study exist [1–8]. In the 18-patient case series by Qiang et al., the mean indwelling time of the ACR was 57 days, ranging from 35 to 123 days [6]. Sancineto et al. published 19 cases with removal of the ACR between 6 and 76 weeks after surgery [7]. Badhra and Roberts reported some difficulties in

the removal of antibiotic nails that have been implanted for more than two months. They found that proximal incarceration of the nail requiring debridement of bone could occur and might need to be addressed using osteotomes [1]. Paley and Herzenberg also retained their cement-coated rods for up to 753 days without any major complication except rod fracture in one patient [5].

There is one study by Selhi et al. in which in some cases of unlocked ACRs were used for infected non-unions and these were retained for a longer period of time in order to achieve bone healing despite the absence of rotational stability. ACRs were kept for a period ranging from 6 weeks to 22 months with an average of 10.6 months [8]. These rods were usually retained until bony union occurred or secondary procedures like external fixation, intramedullary nailing, and/or bone grafting was performed.

2. ACRs can also be used as locked ACR with adequate biomechanical stability in infected long bone non-unions for both local delivery of antibiotics and provision of stable biomechanical conditions for consolidation of the non-union site [9–11]. For this indication, several retrospective case series (with a maximum of 110 cases in one study) exist. Good clinical outcomes with a healed uninfected bone in 105/110 patients (95%) was demonstrated [9]. Removal of the ACR was not reported in the articles and one can assume that the implants were left in place in order to not weaken the bone.

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3.6. TREATMENT: WOUND COVERAGE

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QUESTION 1: Is there evidence to support one type of flap coverage over another (e.g., muscle over fasciocutaneous flap) after open tibial fractures?

RECOMMENDATION: Different types of flap coverage after open tibial fractures have essentially equivalent and comparable outcomes in terms of flap survival, bone healing, stress fracture, infection, chronic osteomyelitis and donor site morbidity. Local flaps should be considered in low energy trauma, when available. The type of flap should be tailored based on the extent and the depth of the soft tissue defect and the location of the fracture. In high energy fractures of the tibia, muscle flaps may offer a more reliable reconstruction with fewer flap failures and fewer reoperation rates.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 95%, Disagree: 5%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

Multidisciplinary management of severe open tibial fractures with radical debridement, skeletal fixation and early stable coverage is essential for infection prevention and high-quality, cost-efficient trauma care [1]. The Gustilo-Andersen grading system of open tibial fractures is a significant prognostic factor of infectious complications and non-unions [2]. Open fractures of the tibia have a high incidence of infection and malunion [3,4]. Wound coverage does not only prevent wound desiccation and infection, but also contributes to fracture repair by serving as a local source of stem or osteoprogenitor cells, growth factors and vascular supply [5,6].

There is a growing body of evidence demonstrating that the biological characteristics of the tissues in a flap can significantly influence fracture healing, and the rate of delayed union or non-union. Timing of soft tissue coverage is also a critical determinant of the length of in-hospital stay and most of the early postoperative complications and outcomes [7]. Early coverage has been associated with higher union rates and lower complication and infection rates compared to those reconstructed after 5-7 days [2,5,7–9]. Furthermore, early reconstruction improves flap survival, as microsurgical free flap integration becomes more challenging with a delay due to an increased pro-thrombotic environment, tissue edema and the increasingly friable vessels. Only those patients presenting to facilities with an actual dedicated ortho-plastic trauma service are likely to receive definitive treatment of a severe open tibia fracture with tissue loss within the established parameters of good practice [7]. "Fix and flap" is being recommended for specialist hospitals where the expertise is available. Antibiotic bead pouches to decrease infection rates have been advocated when there is segmental tissue loss,

gross contamination or established infection as pre-flap tissue infection seems to be an independent predictor of adverse flap and skeletal reconstruction outcomes [10,11].

Fasciocutaneous flaps may be better suited and superior compared to muscle flaps for coverage of the shallow defects at the rapidly uniting metaphyseal fractures around the ankle, particularly with no massive bone or soft tissue loss [6,10,12]. They are easier to monitor postoperatively and tend to have better venous and lymphatic drainage with less acute swelling and better aesthetic appearance [10,13]. Additionally, they become potentially sensate and pedicle-independent from secondary neuro-angiogenesis permitting low-risk flap elevation for subsequent procedures [10,14,15].

Human stromal cells derived from muscle exhibit a significantly greater potential for osteogenesis than those from fasciocutaneous tissue, including both skin and adipose tissue, and are equivalent to those from bone marrow [2,16,17]. Muscle flaps covered with skin grafts in direct apposition with diaphyseal fractures help to obliterate the dead space, reducing potential complications associated with hematoma formation. They may be superior in eliminating bacteria from the wound bed [5] and enhancing healing, but remain pedicle-dependent and difficult to elevate for secondary procedures such as bone grafting. Muscle-only flaps may also have a false high rate of re-operation due to difficult postoperative monitoring. An alternative with the biological benefits of both is a chimeric flap, such as the free anterolateral thigh flap, which includes a segment of *vastus lateralis* [11,14]. Muscle flaps with a cutaneous skin paddle are easier to monitor and thus have a higher salvage rate. Rotational flaps with fasciocutaneous tissue and muscle for proximal defects have shown significantly more complications including infection, necrosis or partial flap loss, compared to free muscle flaps in patients with the most severe grade of osseous injury (44% compared to 23%), and are more likely to require operative re-intervention [6,18].

The selection of proper free flaps for the appropriate defects is also of critical importance, as those with extensive tridimensional tissue loss need free muscle flaps because they conform better to such complex defects [5]. However, free fasciocutaneous flaps are reliable and effective for covering the less three-dimensional distal third and ankle open tibial fractures and can better tolerate the subsequent secondary surgical procedures [11,14,15,19]. It is also important to not underestimate donor-site morbidities [6,13,18]. Surgeon experience and familiarity with the flap should also be an important factor in flap selection. However, the dilemma of choosing between muscle and fasciocutaneous flaps is less relevant than identifying the patient that is at risk of a poor outcome and managing them appropriately [12–14,16]. Finally, there seem to be few significant differences between muscle and fasciocutaneous flaps or between local and free flaps [12,15,19–21]. Although not identified in the Search criteria the following article was felt to be important enough to be included, as it is a recent retrospective study of 39 patients with Gustillo IIIB tibial fractures, muscle flaps may be preferred over fasciocutaneous flaps in these patients. Radiographic assessment of these patients revealed a significantly greater percentage of patients treated with a muscle flap reaching fracture union by six months. There was no statistical difference between muscle and fasciocutaneous flaps at 3 or 12 months though [22]. However, local flaps are preferable in low velocity trauma and free tissue transfer appears to have advantages in high-velocity injuries [10,16].

Published studies on reconstruction of traumatic defects of the tibia are mostly retrospective studies with small, heterogeneous patient cohorts. A few of these compare muscle with fasciocutaneous flaps, but include a wide variety of patients and clinical indications, without sufficient details on the criteria used to select coverage of open tibial fractures [11,12,21]. The outcome measures between studies are different, as not all studies report time to union of the fracture, rates of deep infection or even flap survival. Overall, there is little difference in the clinical outcome with regard to infection rates, wound healing or fracture union, but no study is sufficiently powered to answer these questions. These parameters preclude meaningful systematic review or meta-analysis that can provide standardized guidance for the use of different flap options in the management of open fractures of the tibia [1,11].

To improve the patient's outcome, appropriate international consensus guidelines are required, breaking down also the length of hospital stay and the overall healthcare cost [1].

At this point, based on our understanding of the literature, we believe that different types of flap coverage after open tibial fractures have essentially equivalent and comparable outcomes in terms of flap survival, bone healing, stress fracture, infection, chronic osteomyelitis and donor site morbidity, with the timing of the coverage also being crucial. The type of flap should be based on the extent and the depth of the soft tissue defect, location of the fracture and surgeon experience.

More specifically, if we have to categorize them:

1. In low-energy trauma, local muscle or fasciocutaneous flaps should be considered the reconstruction of choice, if they are available.
2. In high-energy injuries such as open fractures of the tibia, muscle flaps may offer a more reliable reconstruction with fewer flap failures and lower reoperation rates. Free muscle flaps are more advantageous for the reconstruction of tridimensional bone and soft-tissue defects.
3. In patients with simple defects around the distal tibial or ankle, fasciocutaneous flaps may offer a better option.

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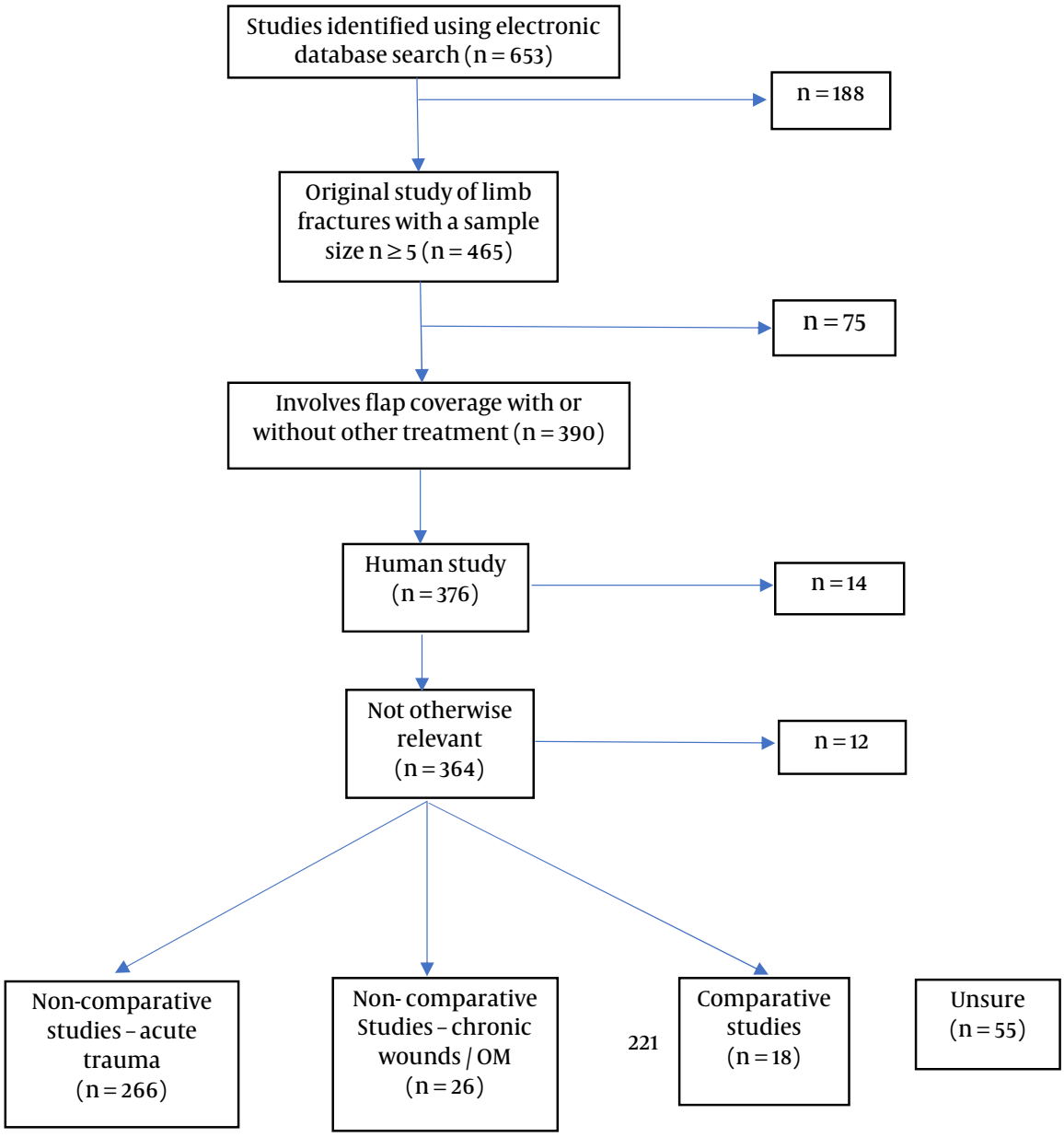

FIGURE 1. Flowchart of literature review.

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QUESTION 2: What is the appropriate timing for flap coverage of open fractures and traumatic wound defects?

RECOMMENDATION: The optimal time for wound coverage ultimately reflects when the wound has been appropriately cleaned and converted to a "living wound." Early flap coverage is preferred, ideally within 3-7 days, when patient and wound are suitable.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 95%, Disagree: 5%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The timing of soft tissue coverage has long been recognized as one of the most critical determinants of the length of in-hospital stay, most of the early postoperative complications and ultimate outcomes [1]. Early coverage has been associated with higher union rates, and lower complication and infection rates compared to those reconstructed after 5-7 days [2–5]. Furthermore, early reconstruction improves flap survival, as microsurgical free flap integration becomes more challenging with a delay due to an increased prothrombotic environment, tissue edema and the increasingly friable vessels. Only those patients presenting to facilities with an actual dedicated ortho-plastic trauma service are likely to receive definitive treatment of a severe open tibia fracture with tissue loss within the established parameters of good practice [6]. "Fix and flap" has sometimes been recommended for specialist hospitals where the expertise is available. Antibiotic bead pouches to decrease infection rates have long been advocated when there is segmental tissue loss, gross contamination or established infection as pre-flap tissue infection seems to be an independent predictor of adverse flap and skeletal reconstruction outcomes [7,8].

Level IV series of free tissue transfer to address open traumatic wounds with accompanying fractures have been published since the first free tissue transfer for soft tissue coverage by Buncke in 1970 [9]. In 1986, Godina advocated early soft tissue coverage on a review of 532 patients based on an increased rate of flap failure in those wounds open > 72 hours [10]. However, during that time period, infection management and particularly the care and treatment of osteomyelitis were poorly understood, and dogma existed that simply the placement of a free tissue transfer over infection in the form of infected hardware or osteomyelitis was enough to treat and cure the infection. It took a great deal of time to break this dogma. Various series advocate the need for early soft tissue coverage in these cases, due to exposed soft tissue as well as the results of higher flap failure and often accompanying late infection rate [11-13]. These studies are found to be flawed in multiple respects, which include the lack of expertise and knowledge in the diagnosis and treatment of existing infection [12], low volume with resultant lack of expertise [11,13] and the inaccurate conclusion that time of flap placement could in any way affect the probability of successful bony union.

Many good studies have appeared confirming what the experienced non-union surgeon and microsurgeon know: that flap survival depends upon a decolonized and "living wound." Harrison et al. performed a thorough literature review of articles published from 1995–2011, and performed meta-analysis of 15 articles meeting inclusion criteria. They reported no difference in outcome between when free tissue transfer was performed and survival of the flap or eventual outcome [14]. Theodorakopoulou et al. reported a systematic review of 11 studies of war-related high energy extremity injuries treated with free tissue transfer in the subacute period (9 days to 3 years post-injury). There was no direct association to time of flap placement with a 95.5% free flap success rate in this particularly complex patient population [15].

Since 2000, numerous independent case series by experienced microsurgeons have also shown no difference in outcome in regard to timing of free flap placement [16-20]. These represent well-executed tissue transfers except for one series with a higher overall but uniform flap failure rate [19]. The consistent finding was that timing of free tissue transfer was not a direct cause of failure of flap survival.

The original work of Godina seems now to be outdated and not applicable to current surgical practice as it relates to timing of free tissue transfer of traumatic wounds.

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Authors: Nathan O'Hara, David Lowenberg, Robert O'Toole

QUESTION 3: Should open fracture wounds be closed primarily or closed secondarily? If closed primarily, which ones and under what criteria?

RECOMMENDATION: Yes. Primary wound closure of many open fracture wounds appears to be a safe and likely beneficial strategy in the modern setting of improved debridement techniques, better methods of fracture stabilization, and improved utilization of early systemic antibiotic administration. It appears safe for lower grade open fractures and a subset of higher-grade open fractures when the wound is deemed appropriate for primary closure on a clinical basis.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

METHODS

Randomized controlled trials, nonrandomized trials, prospective and retrospective observational studies were eligible for inclusion. We searched Medline, Embase, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to March 2018 for published studies without language restriction. Our search strategy, including keywords and MeSH headings, are provided in the Appendix. Eligible studies met the following criteria: (1) all patients included in the study had an open fracture, (2) infection was an outcome variable and (3) there was a comparison between patients with wounds closed primarily and secondary wound closure. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed. The initial search resulted in 303 papers. After removal of duplicates and screening of titles and abstracts, 12 articles were assessed and reviewed.

RATIONALE

The traditional practice of leaving all open fracture wounds open for repeat debridement at a later point in an effort to minimize risk of deep infection has changed over time. Many surgeons now routinely close most open fracture wounds at the time of initial debridement and fixation, particularly in lower grade open fractures and when wound severity and contamination are judged to be appropriate for primary closure.

A systematic review of the literature reveals no level I randomized trials in support of the practice of primary wound closure for open fractures, and the literature supporting this approach is consistently in favor of the practice, but it is also relatively weak. There is a group of more recent studies that has uniformly demonstrated lower surgical site infection rates with primary closure than with secondary closure for various open fractures in adults and children [1–7] and only one older study showing higher infection rates with primary closure [8]. However, all of these studies are methodologically limited as they do not account for selection bias between the less severe wounds that were closed primarily and the more severe wounds that were closed secondarily. As wound severity is very strongly associated with infection rates, this bias is important enough that results from these studies provide only limited insight on this issue except to point out that primary closure of some open fractures does not seem to be associated with high infection rates.

Other authors have provided similar data outlining low rates of infection utilizing a practice of primary wound closure in the vast majority of open fracture cases [9,10]. DeLong et al. used primary closure in 88% of type I, II and IIIA open fractures and had a 4% infection rate [9]. Similarly, Moola et al. used primary closure in 86% of 297 fractures and had a 4.7% deep infection rate [10]. However, while reassuring that primary closure of the majority of open fractures appears to result in an acceptable infection rate compared to historical controls, these studies are similarly methodologically limited as they lack a control group, so it is unknown if a practice of using more secondary wound closures in these patients would have resulted in a higher or lower infection rate.

One double-blind, randomized trial was published in 1993 using a factorial design to compare primary to delayed wound closure as well as the type of antibiotics used [11]. Although the random design is appealing, the sample size of only 82 patients with a low event rate presents a substantial risk of type II error and this study is very underpowered for the outcome of surgical site infection. The cohort only had two deep surgical site infections, so its conclusion that primary closure is safe is reassuring in that there was not a high infection rate in this group, but of limited value in comparing this practice to secondary closure.

The safety of primary closure was also demonstrated in a comparison between two South African trauma centers, one that used primary wound closure and one that did not [12]. This study also concluded that primary closure was safe, but again it was underpowered with a sample size of only 95 patients and an overall infection rate of only 3.3 % (3 patients). Therefore, there is significant risk of type II error with this study, and it therefore cannot provide

sufficient evidence regarding any potential difference in outcomes between the two closure strategies.

Two recent case-controlled studies provide the best evidence in support of this practice while attempting to address the issue of selection bias while also having adequate sample size and event rates to exhibit adequate statistical power. Jenkinson et al. used a propensity-matched cohort study design to demonstrate a lower infection rate in primary wound closure (4%) vs. secondary wound closure (18%, p = 0.0001) even after only including patients matched for likelihood of receiving delayed closure using propensity matching [13]. Scharfenberger et al. collected data prospectively and matched their patients to historical controls from a previous study on factors thought to predict likelihood of surgical site infection and also demonstrated that primary closure had a lower infection risk (4% vs. 9%, p = 0.001) [14]. Although both of these studies are methodologically superior to previous efforts to compare the effect of wound closure strategy on infection rates, the authors point out that there is still risk of unmeasured selection bias and a randomized trial is needed to rigorously compare the efficacy of these two closure strategies.

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APPENDIX – SEARCH STRATEGY (NO PUBLICATION DATE LIMIT)

Ovid Medline – 114 references retrieved on 03/14/2018
((open adj3 fracture*).ab,ti. OR "Fractures, Open".sh.) **AND**
((primary OR delay* OR early OR secondary OR tim* OR definitive OR immediate) adj3 (closure*)).ab,ti **AND**
((infection* or sepsis).ab,ti. or Infection/ or "Wound Infection".sh. or "Cross Infection".sh. or "Sepsis".sh.)

Embase – 147 references retrieved on 03/14/2018
((open NEXT/3 fracture*):ab,ti OR 'open fracture'/de) **AND**
((primary OR delay* OR early OR secondary OR tim* OR definitive OR immediate) NEXT/3 (closure*)):ab,ti **AND**
(infection*:ab,ti OR sepsis:ab,ti OR 'infection'/exp OR 'wound infection'/de OR 'cross infection'/de OR 'hospital infection'/de OR 'sepsis'/exp)

CINAHL – 29 references retrieved on 03/14/2018
((open W3 fracture*) OR MH Fractures, Open) **AND**
((primary OR delay* OR early OR secondary OR tim* OR definitive OR immediate) W3 (closure*)) **AND**
(infection* OR sepsis)

CENTRAL – 13 references retrieved on 03/14/2018 – in Title, Abstract, Keywords
(open NEAR/3 fracture*) **AND**
((primary OR delay* OR early OR secondary OR tim* OR definitive OR immediate) NEAR/3 (closure*)) **AND**
(infection* OR sepsis)

Authors: Daniel R. Schlatterer, Martin McNally, Gerard Chang, James K.K. Chan

QUESTION 4: What are the evidence-based recommendations for the use of negative pressure wound therapy (NPWT) in open fractures and traumatic wounds?

RECOMMENDATION: NPWT is an appropriate dressing in the short-term management (< 7 days) of complex traumatic wounds over open fractures, prior to definite soft tissue closure. NPWT is not superior to other sealed dressings and has increased initial cost.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 86%, Disagree: 9%, Abstain: 5% (Super Majority, Strong Consensus)
Note: Please see Question 2 under Section 1.2. Prevention Risk Mitigation for additional rationale regarding NPWT.

METHODS

A comprehensive literature review was performed to identify all studies on the use of NPWT for the treatment of open fractures and traumatic wounds. We searched Ovid Medline, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to May 2018 for published studies. The search strategy, including keywords and MeSH headings, are provided in the Appendix. Eligible studies

met the following criteria: (1) all patients included in the study had an open fracture or traumatic wound, (2) infection was an outcome variable and (3) NPWT was the intervention. Exclusion criteria were non-English language articles, nonhuman studies, retracted papers, case reports, review papers, studies without clinical follow-up/infection rates, and technique papers without patient data. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria were followed. The initial search resulted in 247 papers. After removal of duplicates and screening of titles and abstracts, 26 articles were assessed and reviewed.

RATIONALE

Traumatic wounds and wounds over open fractures are at increased risk of developing infection due to contamination from injury, impaired blood flow, progressive soft tissue necrosis and prolonged exposure to hospital environment [1]. To minimize this risk, wounds are treated with thorough irrigation and debridement (I&D) followed by primary closure when possible or coverage with a graft or flap. Prior to definitive coverage, traditional occlusive dressings with sterile gauze had been the standard choice. Recently, there has been an increasing trend in using NPWT or vacuum-assisted closure (VAC) for wound management prior to coverage [2]. Proponents of this new method cite the following advantages to support its use: decrease tissue edema, enhance local blood flow, limit or prevent infection, improve flap rates and possibly reduce the overall need for flaps.

We performed a systematic review of the literature, as detailed above, to determine the evidence-based role of NPWT in the treatment of traumatic wounds and open fractures.

We found a group of studies supporting the use of NPWT in the treatment of traumatic wounds and open fractures. The study populations were a mix of children and adults with either traumatic wounds or open fractures, all of whom received NPWT. They found that NPWT was safe and effective and resulted in similar or lower infection rates, reduced flap complications, reduced graft size and decreased need for free flaps compared to historic controls [3–10]. However, while promising, all the studies were retrospective case series that were methodologically limited in that they lacked a comparative group and were retrospective in nature.

Eight studies compared NPWT to traditional gauze in the management of acute traumatic wounds or open fractures. Five were prospective randomized control trials, and three were retrospective case control studies. The three retrospective studies evaluated open tibia fractures and found NPWT to have significantly lower rates of infections (8.4-10 % vs. 22.6-33%), wound complications and flap failures compared to traditional gauze [11–13]. These findings are encouraging but are susceptible to the inherent limitations of retrospective studies, most notably selection bias.

The best evidence to support NPWT was found in four prospective randomized control trials comparing NPWT to traditional gauze in patients with acute traumatic wounds or open fractures. Three studies evaluated infection rate as an outcome. Two of the 3 studies showed significantly decreased infection rate with NPWT (4.6-5.4% vs. 22-28%) compared to gauze [14,15], while the other study found no difference between the two [16]. With regards to healing time, 2 of the prospective randomized control trials studied time to granulation as an outcome and both showed NPWT to be superior to gauze dressings [16,17].

With regards to duration of NPWT treatment, 3 studies retrospectively evaluated cases of traumatic wounds or open fractures treated with < 7 days of NPWT prior to wound coverage versus > 7 days of NPWT prior to wound coverage and compared them in terms of infection rate and reoperation rate. All 3 studies found a higher infection rate in cases treated with > 7 days of NPWT and concluded that while NPWT can be helpful in the management of traumatic wounds, its use should be limited to < 7 days or risk of infection increases [18–20]. However, all of these studies are methodologically limited, as they do not account for selection bias between the less severe wounds that were covered earlier and the more severe wounds that required longer time until coverage. As wound severity is very strongly associated with infection rates, this bias is important enough that results from these studies provide only limited insight on this issue. Another retrospective case series evaluated open fractures treated with I&D and NPWT prior to flap coverage. All patients had > 3 days, mean 18 days, of NPWT as they were treated on a delayed basis following stabilization and then transfer to their referral center for coverage. They found low rates of flap loss and infection, comparable to historical controls of patients treated with less than three days before definitive coverage [21].

There is an increasing body of data supporting NPWT as an adjunctive modality at all stages of treatment for traumatic wounds and open fractures. There is an association between decreased infection rates and decreased healing time with NPWT compared with gauze dressings. There is evidence to support NPWT beyond 72 hours without increased infection rates although prolonged use greater than 7 days may actually increase the risk of infection. At this time, NPWT use for traumatic wounds and open fractures requires extensive additional study.

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APPENDIX – SEARCH STRATEGY

Ovid Medline 221: (((open adj3 fracture*) or trauma*) adj3 wound*).ab,ti. or ("Fractures, Open".sh. or soft tissue injuries/) **AND** (NPWT or negative pressure wound therapy or VAC or (vac* adj3 clos*)).ab,ti. or negative-pressure wound therapy/**AND** ((infection* or sepsis).ab,ti. or Infection/ or wound healing/ or "Wound Infection".sh. or "Cross Infection".sh. or "Sepsis".sh.)

Scopus 25: (open W/3 fracture* OR trauma* W/3 wound*) AND (npwt OR {negative pressure wound therapy} OR vac OR vac* W/3 clos*) AND (infection* OR sepsis OR wound* W/3 heal*)) in TITLE-ABS-KEY

CENTRAL 21: (open near/3 fracture* OR trauma* near/3 wound*) and (npwt OR "negative pressure wound therapy" OR vac OR vac* near/3 clos*) and (infection* OR sepsis OR wound* near/3 heal*) in in Title, Abstract, Keywords
Combined: 237

3.7. TREATMENT: OUTCOMES

Authors: Mustafa Citak, Carl Haasper, Kenneth Egol, William T. Obremskey, Hussein Abdelazia, Philip Linke

QUESTION 1: What is the most appropriate outcome measurement (clinical, radiographic, laboratory, etc.) for management of early infection after fracture fixation (IAFF)?

RECOMMENDATION: Fracture healing and infection control seem to be the most appropriate outcome measure to monitor the response to management of early IAFF. Secondarily, treatment success following infection management after fracture fixation is best assessed using a combination of the patient's clinical picture and laboratory examinations such as tissue cultures, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 70%, Disagree: 10%, Abstain: 20% (Super Majority, Weak Consensus)

RATIONALE

Regardless of the fracture site, primary fixation method, depth of the infection, culture results, nature of the fracture (closed or open) or chosen treatment algorithm for management of the infection, fracture healing seems to be the most appropriate final outcome measure for the treatment of an early IAFF. It must be noted that there remains substantial heterogeneity with wide variability in the definition of an early infection with regard to the time of its onset.

IAFF is one of the most serious complications in orthopaedic trauma surgery, which can impair fracture union, lead to poor functional outcomes or even result in loss of the extremity [1,2].

The management of IAFF and that of periprosthetic joint infection (PJI) differs from each other in some aspects. When treating an early IAFF, the primary aim should be the achievement of fracture healing to avoid delayed union or nonunion rather than immediate eradication of the infection [1,3].

Complicating infection management is the fact that there is no clear consensus with respect to what constitutes treatment success. Previous studies have defined the success of infection management based upon factors such as bony healing, clinical examination, culture results and the laboratory markers ESR and CRP.

To identify the best available outcome measure for the management of early infections after fracture fixation, we included all publications that reported on outcomes following management of early IAFF [4–37]. However, we found substantial heterogeneity in the definition of an early infection with regard to the time of its onset, one that varies from two weeks to five months [4,6,10,12,16,18,22,25–28,31].

Several papers reported on the clearance of the infection or its recurrence, either exclusively or with further outcome measures; other studies on the functional and clinical outcome or on the wound and soft tissue healing and few studies on the mortality rate. There are only limited number of reports on laboratory, microbiological or histological investigations as outcome measures [33,35–37].

It is important to note, that any cause of inflammation will trigger an increase in the patient's ESR and CRP. For example, surgery-related tissue damage and practices such as reamed intramedullary nailing have been shown to trigger a systemic inflammatory response and can lead to elevated ESR and CRP in the early postoperative period [36,37]. While the sensitivity of acute phase reactants for the presence of inflammation is high, non-infectious etiologies must always be considered. Recent studies have demonstrated that tissue

histology is one option for the confirmation of infection when tissue cultures are inconclusive; however, this technique is labor intensive and also prone to false negative findings [33,35].

The most common outcome measure in most studies was fracture healing or bony union [4–32]. The vast majority of identified studies have only a low to moderate level of evidence with retrospective case series designs and relatively small sample sizes. Moreover, measuring the outcome of a specific management strategy was the main focus of only a few studies. Regardless of fracture site, primary fixation method, depth of the infection, culture results, nature of the fracture (closed or open) or chosen treatment algorithm for the infection, outcome measures were extracted and analyzed. Due to the considerable heterogeneity, some descriptive analysis was also performed [4–32].

There were five studies with a relatively large case series. Rightmire et al., Berkes et al., Al-Mayahi et al., Hellebrekers et al. and, recently, Kuehl et al. reported on the outcomes after management of an early or acute IAFF of upper and lower extremity as well as pelvis and spine within the first four months in 69 patients, six weeks in 123 patients, five months in 71 patients, three months in 44 patients and three weeks in 49 patients, respectively. Besides the cure of the infection, fracture union was an important outcome measure in three of them. In the studies by Hellebrekers et al., Berkes et al. and Rightmire et al., in which open fractures were also included, fracture union was achieved in only 63%, 71% and 68% with implant retention, respectively. Implants had to be removed due to recurrence of infection in many cases [4,16,21,25,27].

The failure rate following IAFF of the ankle was 28% among the early infected cases (within the first six weeks), which could be related to persistence of the infection, a non-union or post-traumatic arthritis [22]. In the study by Zalavras et al., infection recurred in three of four identified infections within the first three weeks after ankle fracture fixation that had been managed with debridement and retention of the implant [9]. In contradistinction, Ziegler et al. have recently reported a 100% success rate with healing of ankle fractures without remissions following debridement and retention following IAFF that definitely occurred within three months after surgery [14].

Regarding IAFF with intramedullary nailing of the femur and tibia, there was only one infected non-union case from a total of 13 acute infections within the first month in the retrospective study performed by Chen et al. There was no significant difference regarding the time to fracture healing between cases with retention of the nail and those with nail exchange [31]. Among the included patients with infected intramedullary nails in the three older studies, only a few cases with an early infection within the first three weeks could be identified and delayed union had been observed [11–13].

In another prospective multicenter cohort study reporting on IAFF of the tibia, 56% of the fractures healed radiographically at one year, compared to 88% of those that were uninfected, and the time to union was significantly longer than that for the noninfected fractures. However, only 5 from 23 infected cases were reported to be early infections [15]. Delayed union was also observed in 3 out of 15 infected tibia and femur fractures treated with non-contact plates due to IAFF within 10 weeks after primary surgery [19].

Short- and long-term mortality rate was the outcome measure following management of IAFF within three months after surgery of the hip in the retrospective studies by Duckworth et al. and Edwards et al. [24,26]. Partanen et al. also performed a similar but matched control analysis although not all included cases were early infections. Beside the functional outcome and mortality rate, fracture healing was also analyzed. Failure to union was observed in 8 out of 19 cases, as infection most likely impaired fracture healing [29].

Deep early IAFF of proximal or distal humeral fractures treated by plate osteosynthesis had a high non-union rate, resulting in a poor functional outcome [20,28].

Pin tract infections in the form of K-wire fixation or external fixators can be managed conservatively and spontaneous fracture healing can be achieved with resolution of the infection [7,17,23].

Fracture union was also the common outcome measure to assess the success of management of IAFF of flat bones including the ribs, clavicle or mandible [5,18,30,32]. It can be evaluated both clinically and radiologically [5,10,14,16,17,25].

Even in late phases, the eradication of infection with restoration of an acceptable functional outcome is definitely the ultimate goal when treating an IAFF. Regardless, at this time fracture healing seems to be the most appropriate outcome measure in the case of an early infection. As soon as fracture healing is achieved, removal of the implant for the purpose of definitive eradication of infection can be considered.

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PART XI

BIOFILM

Section 1: Formation

Section 2: Disruption

Formation

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QUESTION 1: What is the life cycle of biofilm and the mechanism of its maturation?

RESPONSE: A biofilm may be defined as a microbe-derived sessile community characterized by organisms that are attached to a substratum, interface or each other are embedded in a matrix of extracellular polymeric substance and exhibit an altered phenotype with respect to growth, gene expression and protein production. The biofilm infection life cycle generally follows the steps of attachment (interaction between bacteria and the implant), accumulation (interactions between bacterial cells), maturation (formation of a viable 3D structure) and dispersion/detachment (release from the biofilm). The life cycle of biofilm is variable depending on the organism involved. There are characteristics in the life cycle of biofilm formation. These include attachment, proliferation/accumulation/maturation and dispersal. Biofilm can either be found as adherent to a surface or as floating aggregates.

LEVEL OF EVIDENCE: Strong (this is a scientific review)

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

PRE-MEETING RATIONALE

To answer this question the authors searched Pubmed and Google Scholar between January 1950 – August 2018. Search words included: biofilms, biofilm formation, bioflm life cycle, staphylococci biofilms, Gram positive organisms, pseudomonas aeruginosa biofilms, antibiotic resistance and prosthetic joint infections (PJIs). Relevant papers based on the above search words were reviewed.

Most studies found were animal studies, laboratory studies, in vivo studies and a few clinical studies. Due to time constraints, complete systematic review of the literature could not be performed.

A biofilm may be defined as a microbe-derived sessile community characterized by cells that are attached to a substratum, interface or each other are embedded in a matrix of extracellular polymeric substance and exhibit an altered phenotype with respect to growth, gene expression and protein production [1]. Biofilm thickness can vary between a single cell layer to a thick community of cells embedded within a polymeric matrix. Recent structural analyses have demonstrated that these biofilms possess a sophisticated architecture in which microcolonies can exist in discrete pillar or mushroom-shaped structures [2]. Between these structures, an intricate channel network provides access to environmental nutrients.

PJI can be initiated through hematogenous spread or by direct seeding via an overlying infection, penetrating trauma or contamination during surgical implantation of the prosthesis. Regardless of the seeding source or microbial species, the stepwise progression of the infection is dependent upon biofilm formation and maturation.

The biofilm infection life cycle generally follows the same steps of attachment (interaction between bacteria and the implant), accumulation (interactions between bacterial cells), maturation (formation of a viable 3D structure) and dispersion/detachment (release from the biofilm). This progression is mediated by the interplay of a number of microbial, host and environmental factors, and these are usually different in varying microbial species or even strains within species. A rapid stage progression can be seen with virulent, biofilm-forming pathogens in a susceptible host (e.g., a virulent *Staphylococcus aureus* (*S. aureus*) strain in a host with immunosuppression). In contrast, an infecting microbe with slow growth and low virulence (e.g., *Cutibacterium acnes* – formerly *Propionibacterium acnes*) in a healthy host capable of suppressing biofilm formation can produce an indolent infection with delayed progression.

By adopting this sessile mode of life, biofilm-embedded microbes enjoy a number of advantages over their planktonic counterparts. One advantage is the ability of the polymeric matrix to capture and concentrate a number of environmental nutrients, such as carbon, nitrogen and phosphate [3]. Another advantage to the biofilm mode of growth is it enables resistance to a number of removal strategies, such as antimicrobial and antifouling agent removal, shear stress, host phagocytic clearance and host oxygen radical and protease defenses. This inherent resistance to antimicrobial factors is mediated in part through very low metabolic levels and drastically down-regulated rates of cell division (e.g., small colony variants) of the deeply embedded microbes [4]. While low metabolic rates may explain a great deal of the antimicrobial resistance properties of biofilms, other factors may play a role as well. One such factor may be the ability of biofilms to act as a diffusion barrier to slow down the penetration of some antimicrobial agents [5]. For example, reactive oxidative species may be deactivated in the outer layers of the biofilm, faster than they can diffuse into the lower layers [6].

The last advantage of the biofilm mode of growth is the potential for dispersion via detachment. As mentioned, micro-colonies can exist in discrete, mushroom-shaped structures. These microcolonies may detach under the direction of mechanical fluid shear or through a genetically programmed response that mediates the detachment process [7]. Under the direction of fluid flow, this microcolony travels to other regions of the host to attach and promote biofilm formation on virgin areas. Therefore, this advantage allows a persistent bacterial source population that is resistant to antimicrobial agents and host immune clearance, while at the same time enabling continuous shedding to promote bacterial spread.

S. aureus Biofilm Formation

Although many bacterial pathogens are capable of forming biofilms in a range of clinical contexts, *S. aureus* is the main etiological agent associated with PJI.

The initial phase of biofilm formation is characterized by the attachment of planktonic cells to a surface. In a planktonic mode of growth, *S. aureus* up-regulates the expression of key mediators for immunoavoidance (e.g., Protein A) and the attachment to biotic surfaces. These mediators are a variety of proteins anchored in the

cell wall, the largest group of which are termed microbial surface components recognizing adhesive matrix molecules (MSCRAMMs) [8]. Binding of MSCRAMMs to host components such as fibronectin, fibrinogen, collagen and cytokeratin are an important first step in the attachment of *S. aureus* to initiate biofilm formation [9]. Attachment to abiotic surfaces is also determined by properties and physicochemical characteristics of the abiotic surface as well as the bacterial surface, with hydrophobic and electrostatic interactions playing a major role [10].

However, it is worth noting that many abiotic surfaces, as is the case with many implanted medical devices, are rapidly coated in host matrix components upon implantation. Therefore, surfaces that have been engineered to be "biofilm-resistant" have failed in vivo since *S. aureus* mediates attachment to these conditioned surfaces [11]. The presence of a devitalized surface coated with host extracellular matrix proteins decreases the infectious dose required to cause infection to less than 100 viable *S. aureus* cells, thereby increasing the ability of *S. aureus* to cause biofilm infections by over 75,000 fold [12].

Following this initial attachment, bacteria proliferate and produce an extracellular matrix (ECM), often referred to as slime or glycocalyx, comprised of proteins (both host derived and bacterial), carbohydrates and extracellular DNA (eDNA). These serve as a scaffold for maturation and 3D structuring of the biofilm [11]. Ultimately, through coordinated degradation of ECM via proteases, nucleases, delta hemolysin and other factors (e.g., phenol soluble modulins), bacterial cells are released from the biofilm with the potential to seed secondary sites of infection [13]. Below is a brief discussion of the factors and mechanisms responsible for these stages of the *S. aureus* biofilm life cycle.

The next phase of biofilm formation entails the proliferation and accumulation of attached bacterial cells. During this early phase, intercellular attachment plays a key role in stabilizing the early biofilm before a significant amount of ECM can be produced to protect the attached cells from disruptive forces such as shear force [11]. One key contributor to intercellular adhesion is the polysaccharide intercellular adhesin (PIA), first studied in *Staphylococcus epidermidis* [14]. The MSCRAMMs (discussed above) and certain cytoplasmic proteins shown to bind to eDNA are also know to contribute [15–17]. Together, these factors not only play a role in early intercellular adhesion but also constitute major components of the ECM produced by biofilm-associated cells.

Recent studies utilizing technology allowing for nearly real-time evaluation of biofilm progression have suggested the addition of a stage of biofilm development following proliferation/accumulation referred to as an "exodus" phase [18]. This exodus phase is characterized by an early dispersal event with a reduction in total biomass from a biofilm. This is reportedly achieved through the coordinated bacterial expression of secreted nucleases by a subpopulation of bacterial cells resulting in degradation of eDNA and subsequent bacterial release [18]. The purpose of this phase and its necessity for the overall progression of the biofilm life cycle remain to be determined. However, given the timing of these observations within the overall progression of biofilm formation, it has been suggested that a dynamic shift occurs in which early events are largely protein-mediated and subsequent events are mediated by both protein and eDNA [11]. Although some literature would suggest that certain biofilms tend to be exclusively dependent upon PIA, protein or eDNA, these studies propose a more dynamic model of development with temporal and spatial changes in ECM components [11].

The maturation phase of the biofilm life cycle entails the 3D structuring of biofilms into classic architectural structures (towers and mushroom-like structures) and the development of microcolonies displaying some degree of phenotypic diversity [10,11]. This complex structuring is coordinated through the balance of adhesive and disruptive factors [10]. Adhesive factors include the ECM components discussed above such as PIA, proteins and eDNA. Disruptive factors include enzymes that degrade these components such as proteases and nucleases, as well as the surfactant-like molecules, phenol-soluble modulins (PSMs). These disruptive factors allow for the remodeling and maturation of biofilm structures. For example, studies have demonstrated that channels are created throughout a biofilm via the surfactant-like activity of PSMs, allowing nutrients to reach deeper layers of the biofilm [19]. Therefore, these studies describe biofilm maturation as a subtractive process. Alternatively, some studies suggest an additive process of maturation from observations of microcolonies emerging from slower growing basal layers of biofilms [20]. It is likely that both additive and subtractive processes contribute to the complex structuring observed during biofilm maturation.

The final step of the biofilm life cycle involves the dispersal of cells with the ability to travel to distal sites to disseminate infection. The mechanism by which *S. aureus* regulates this step is largely mediated by the accessory gene regulator (*agr*) quorum-sensing system [19,21]. The *agr* system responds to cell density through the accumulation of signal molecules, allowing for dispersal to occur once a threshold density is reached [22]. The *agr*-regulated factors that have been proposed to mediate dispersal include secreted proteases and resultant degradation of protein components of ECM [23]. Dispersal has also been proposed to be mediated by the *agr*-mediated production of PSMs, which act by disrupting molecular interactions within biofilms [19].

In addition to these staphylococcal factors responsible for PJI development, the complicit nature of the host towards biofilm formation also plays a role. In an early *S. aureus* biofilm infection, the intense inflammatory response is produced by the host. *S. aureus* is readily able to resist clearance from the host through a large number of virulence factors that specifically attack the host and promote immunoavoidance. The expression of *S. aureus* virulence factors, timed by the quorum sensing system, promotes the host to release T_H1 cytokines, including interleukin (IL)-12, interfenn gamma (IFN-γ), tumor necrosis factor alpha (TNF-α), and IL-17 resulting in a shift of the adaptive immune system to an ineffective T_H17 and T_H1 cell-mediated immune response. This type of response is incapable of clearing a biofilm infection, thereby enabling *S. aureus* to form a fully mature biofilm and a persistent infection. The other branch of adaptive immunity, the T_H2 antibody-mediated response, is readily effective at clearing the infection in the early phase of biofilm formation before it progresses to a fully mature phenotype. However, this antibody-mediated response is shut down both by the host cytokines associated with the initial response to *S. aureus*, most notably IFN-γ, and by the *S. aureus* production of superantigens, capsule and other toxins. Additionally, *S. aureus* produces a number of highly immunogenic decoy antigens (e.g., lipase) that augments the ability of *S. aureus* to cause disease and reduces antibody production against more vital antigens [24]. By the time the antibody-mediated immune system recovers and mounts an effective response against the biofilm infection, the fully mature biofilm is able to resist clearance. Even if cleared through surgical intervention and infection resolution, this host immune response manipulation and variable antigen expression allows *S. aureus* to re-infect patients throughout their lifetime.

Once in this fully mature phase, the infection can remain quiescent for years or even decades, or more typically, will show remarkable signs of chronic inflammation [25]. This host response is often due to the metastasis of metabolically active and virulent planktonic subpopulations that have dispersed/detached from the localized biofilm aggregate. Antibiotic therapy is effective against these

active populations allowing for temporary suppression of clinical signs and symptoms of the underlying biofilm disease. However, upon antibiotic treatment cessation, exacerbation of the disease will necessarily result.

Biofilms Formed by Other Microbial Species

In addition to *S. aureus*, a number of other microbial species are able to form infectious biofilms in PJIs [26]. These include other facultative anaerobic, gram-positive, non-motile bacterial species, including coagulase negative staphylococci and *Streptococcus* and *Enterococcus* species. The stages of biofilm formation are similar, and these microbes use a number of homologs to the biofilm-associated virulence factors already described for *S. aureus*. Species other than these gram-positive microbes contribute towards PJI, particularly the facultative anaerobic gram-negative bacilli, including *Escherichia coli* and *Pseudomonas aeruginosa* and anaerobes to a lesser extent.

Gram-negative bacterial biofilms, especially *P. aeruginosa,* have long been studied in the biofilm research field due to their ubiquitous nature in the environment and disease, and their preponderance in chronic wounds and cystic fibrosis lung infections. Although the stages progress through early attachment, mature attachment, accumulation, maturation and dispersion/detachment, the mechanisms by which these steps are accomplished show important differences to gram-positive pathogens.

The motility provided through flagella allows *P. aeruginosa* to facilitate close association with surfaces, such as those in indwelling medical devices. The microbial cells will then proceed to irreversible attachment. Additionally, Type IV pili provide for differential virulence factor production associated with shear stress as well as allow subpopulations to migrate on the surface through twitching motility. As the biofilm accumulates, the formation of complex multicellular structures occurs that demonstrate heterogeneity of nutrients, pH and oxygenation. During maturation, the development of membrane blebs, nanofilaments, eDNA structural support and electrical coupling of the embedded bacterial cells also occurs. As the population swells, the homoserine lactone quorum sensing system induces the production of the surfactant and anti-leukocyte pseudomonal rhamnolipids to prevent clearance and add to the burgeoning inflammatory response. The microbes can then either disperse as single-celled planktonic populations or detach from the biofilm in large conglomerated flocs that allow for metastasis of the infection while enjoying the protective environment of the biofilm matrix.

Clinical Relevance: Treatment and Resolution

During the early acute stage of infection and inflammation, the biofilm is in an early accumulation phase. During this phase, the growing biofilm demonstrates higher susceptibility to antimicrobial therapy than the fully mature, quiescent and metabolically inactive biofilm phenotype. This increased susceptibility to antimicrobial therapy during the acute phase of PJIs translated into efficacious treatment without surgical intervention [28]. When effective combination antimicrobial therapy was used alone to treat PJIs with clinical signs of less than one month in duration, over 83% of patients were successfully treated without surgical intervention. However, once symptoms lasted for greater than six months, successful treatment of antibiotic therapy fell to just over 30%. Therefore, the potential for effective therapy of PJIs without surgical intervention may be a possibility if the infection is diagnosed early and targeted antibiotic therapy is quickly initiated with emphasis on adding Rifampin/Rifampicin when a *Staphylococcus* spp is the etiological agent. After this early therapeutic window, proper surgical debridement along with combination antibiotic therapy is necessary for optimal infection resolution.

Clinical Relevance: Diagnosis

Rapid, effective and sensitive discovery and identification and antibiotic sensitivity determination of the pathogenic bacterial species must be accomplished in order to effectively combat PJIs. Once identified, effective therapeutic counter-measures and treatment can be applied. Currently, pathogen identification requires microbial culture followed by diagnostic analyses that normally require additional rounds of replication in culture or purification of specific bacterial/fungal products. At best, microbial identification may require days to weeks, depending on the growth rate of a specific pathogen. These limitations of bacteria are dramatically exacerbated in diagnosing and speciation of the etiological agent in PJIs. Culture from tissue samples can be effective during the early stages of infection when the biofilm is in an accumulation phase and planktonic populations are present. However, all too often, patients have received antimicrobial therapy prior to proper tissue sampling, thereby eliminating the easily detected planktonic populations, leaving behind only small microbial aggregates that are often missed during biopsy. Also, as the biofilm matures, the host immune response walls off the infectious nidus to form these same hard-to-detect biofilm aggregates.

In conclusion, understanding the progression of biofilm life cycles and the mechanisms that pathogens use to regulate this progression is essential for the development of therapeutic approaches aimed at preventing, disrupting and eradicating biofilm-associated infections.

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QUESTION 2: What surface properties favor biofilm formation?

RESPONSE: The attachment of bacteria to implant and biological surfaces is a complex process, starting with the initial conditioning film. Roughness, hydrophobicity/hydrophilicity, porosity, pore topology and other surface conditions are the key factors for microbial adhesion. Because of the huge variety of these factors, most of the studies directed at bacterial attachment to the implant surface were limited to specific surface conditions since it is difficult to examine the plethora of parameters concomitantly. There are variable conclusions among the available basic science and animal studies relevant to this topic, many of which will be described in greater detail below. Bacteria can form biofilm on almost all prosthetic surfaces and biological surfaces. To date, this consensus group knows of no surface that is inimicable to the growth of biofilm in vivo.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

PRE-MEETING RATIONALE

Bacterial biofilms are widely known to contribute to the etiology of chronic infections and implant-associated infections. Biofilm development commences upon formation of a conditioning layer conducive to bacterial attachment, the attachment itself and secretion of a slime-like substance [1]. It is this secretion that enables biofilm formation and ultimately introduces antibiotic resistance and resistance to the host immune system. Several surface properties have been identified that can influence biofilm formation, these include: surface chemistry and functional groups, surface free energy and level of hydrophilicity/hydrophobicity, surface charge, micro- and nano-topography and porosity. Surface chemical composition, micro-roughness and surface free energy would appear to prevail for importance [2].

There is strong evidence that the initial attachment of bacterial species to the surface of a biomaterial is influenced by the presence of adsorbed proteins [1,3]. Wagner et al. [1] found that titanium surfaces preconditioned through exposure to blood plasma enhanced bacterial adhesion for both *Pseudomonas aeruginosa* and *Staphylococcus aureus (S. aureus)*. Likewise, a study performed by Frade et al. presented similar findings with respect to surface adhesion of *Candida albicans* (*C. albicans*) and subsequent biofilm formation on multiple surfaces after serum coating, including polycarbonate, polystyrene, stainless steel, Teflon, polyvinyl chloride and hydroxyapatite [3].

Similarly, there is also strong evidence supporting the conclusion that bacterial adherence and biofilm formation increase with the roughness of the implant surface [4,5]. A study conducted by Karygianni et al. found that *Enterococcus faecalis, S. aureus,* and *C. albicans* adhered more to a rougher implant surface relative to a smoother surface [5]. Furthermore, Braem et al. demonstrated that a porous surface coating was more susceptible to biofilm formation than a smoother titanium-based surface after exposure to *S. aureus* and Staphylococcus epidermidis *Staphylococcus epidermidis* (*S. epidermidis)* [4].

A small number of studies have also examined the impact of the hydrophobicity/ hydrophilicity of implant materials on subsequent biofilm formation [2,3,6]. For example, a study performed by Koseki et al. using *S. epidermidis* showed decreased biofilm formation on cobalt-chromium-molybdenum alloy (Co-Cr-Mo) which was attributed to its increased hydrophobicity [2]. However, two other studies showed contrary results. For instance, *C. albicans* was shown to have less metabolic activity on polycarbonate and stainless steel (hydrophilic surfaces) relative to Teflon (hydrophobic surfaces) [3]. Similarly, some studies contend that hydrophilicity has only trace impact on biofilm formation, as shown by the fact that *S. epidermidis* biofilm formation was not significantly altered by differences in surface wettability [6]. With that, findings remain inconclusive as a whole concerning the impact of implant surface hydrophilicity/hydrophobicity on biofilm formation.

Finally, there are various surface properties that are given moderate recommendations here due to their high-quality evidence but low replication in the studies presented. The first is that surface

nanostructures, such as projections and recesses, reduce overall bacterial adhesion and biofilm formation compared to smooth surfaces [7]. The second is that low nanostructure stiffness inhibits biofilm accumulation, likely due to the susceptibility of these nanostructures to shear forces [8]. The third is that calcium-incorporated oxide coatings on a titanium surface reduces bacterial colonization when compared to non-calcium modified titanium. This is due to calcium drastically decreasing the contact angle [4].

Although there is little consensus in terms of which surface properties are most definitive in contributing to biofilm formation, there are certainly strides in examining the general impact of different properties when considered individually. Due to the complexity of biomaterial properties inherent to orthopaedic implant structure—and the lack of agreement among the literature concluding the impact of these properties—we conclude that biofilm formation is favored by combinations of surface parameters, and so should be assessed as such in the development of biofilm resistant implants. Furthermore, there are few studies examining the impact of surface properties in biofilm formation among human subjects postoperatively and further clinical studies are necessitated.

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QUESTION 3: Is the biofilm on orthopaedic implant surfaces permeable to neutrophils and macrophages in vivo? Are these innate immune cells (meaning any macrophages or neutrophils) capable of engulfing and killing bacteria?

RESPONSE: A mature bacterial biofilm has limited permeability to neutrophils and macrophages. Those that get through are clinically ineffective at eradicating biofilm bacteria. While neutrophils and macrophages are capable of engulfing and killing planktonic bacteria, they are not innately capable of effectively engulfing and killing sessile bacteria in biofilm.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

PRE-MEETING RATIONALE

The most important pathogenic mechanism involved in implant-related infections is the ability of the microorganisms to form a biofilm [1], which leads to protection against environmental stress, host immune defense and antimicrobials [2]. The first cells arriving at the infection site are the neutrophils and macrophages [3]. The permeability and the phagocytosis ability of these immune cells have mainly been evaluated in two types of infection: cystic fibrosis [4–8] and device related infection, mainly catheter-related infection [9–17] and periprosthetic infection [18].

Neutrophils are innate immune cells capable of secreting an arsenal of toxic oxygen species, degrading enzymes, defensins and lipid inflammatory mediators to fight off infection [6]. These cells have shown the ability of sticking but not penetrating into a mature biofilm and phagocytizing biofilm encased microorganisms [4–8,10,11,14,19–23]. The exopolymeric substances of the biofilm matrix seem to be involved in the formation of neutrophil extracellular traps in biofilm of *Streptococcus suis* [21], *Candida albicans* [10] and *Candida glabrata* [11]. Data shows that neutrophils can destroy a two to six day old *Staphylococcus aureus* (*S. aureus*) biofilm, but a mature biofilm is capable of resisting penetration by these cells [24].

Guenther et al. studied the different behavior of polymorphonuclear neutrophils (PMNs) towards the biofilm formed by either *S. aureus* or *Staphylococcus epidermidis* (*S. epidermidis*). In the case of biofilm formed by *S. aureus*, the PMNs were observed to move across and scavenge bacteria along their path. Conversely, PMNs in contact with *S. epidermidis* biofilm were nearly immobile and phagocytized only bacteria in close proximity. Why biofilms of *S. aureus* appear more sensitive to a PMN attack compared to those produced by *S. epidermidis* is not well understood [19]. Insights on the behavior of biofilm formed by *S. epidermidis* have been offered by the in vitro and in vivo studies of Kristian et al. These authors found that *S. epidermidis* biofilms triggered higher levels of complement activation in terms of C3a formation than planktonic wild-type bacteria and isogenic ica-negative bacteria. On the other hand, a decreased deposition of immunoglobulin G (IgG) and C3b was observed in biofilm-embedded bacteria. This could possibly explain the evasion of PMNs killing [25].

Alhede et al. evaluated the role of immune system against biofilm formed by *Pseudomonas aeruginosa*. They demonstrated that both in vitro and in vivo biofilms of *Pseudomonas aeruginosa* produce

a shield of excreted rhamnolipids, which offers protection from the bactericidal activity of PMNs [26].

Arciola et al. did an extensive study of biofilm formed by Staphylococcus on an implant surface. Based on their work, PMNs were found to surround biofilm and become activated, but PMNs were not able to migrate into the biofilm, probably because of a lack of a chemotactic signal as well as by hindrance of migration into the "slimy" material. Thus, the inability of PMNs to penetrate biofilm results in progression of implant related infections. The activation of PMNs and their attempt to kill bacteria results in secretion of numerous cytotoxic and proteolytic enzymes that cannot act against bacteria but results in damaging and destroying the surrounding host tissues [27].

Macrophages become the prevailing cells and remain at the infection site a high concentration for several weeks and they are related to recognition, phagocytosis, secretion of enzymes, cytokines, chemokines and growth factors, to destroy and digest the phagocytized pathogens [3]. These cells can penetrate into a mature biofilm in a similar way as neutrophils, and phagocytize biofilm encased microorganisms, but not destroying them [9,12,13,18]. Moreover, these sessile phagocytized bacteria can even persist into peri-implant tissue inside macrophagic cells not only in experimental models, but also in the tissues of patients with intravenous catheters colonized by different bacteria [16,17]. *S. aureus* prosthetic infection in vivo model showed that limited bacterial macrophage uptake is due to inflammatory attenuation by *S. aureus* biofilm [13], which favor the transformation from M1 macrophages presents a high antimicrobial activity to M2 type inherently possesses less antimicrobial activity [13], and the cell death induction though leukocidin A/B [28] and human leukocyte antigen production [18]. At the site of staphylococcus biofilm infection, macrophages exhibit: down-regulation of interleukin (IL)-1β, tumor necrosis factor, CXCL2 and CCL2 expression, reduced bacterial uptake, minimal iNOS expression and consequent low efficiency in killing phagocytized bacteria and reduced induction of lymphocyte production of interferon-γ. These scavenging cells appear able to migrate into the biofilm but cannot clear the site from the pathogen causing the infection as their bactericidal activity appears compromised [27].

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QUESTION 4: Does the timescale of biofilm formation differ between bacterial species? If so, what is the timescale for common causative organisms?

RESPONSE: Currently, there is no clinical research available to answer whether the timescale in the development of biofilm formation differs between bacterial species. In vitro studies show high variability in biofilm formation based on bacterial strains and conditions. Animal studies have demonstrated rapid (minutes to hours) biofilm formation. The group notes that the timeline of biofilm formation may not correlate with the onset of infection symptoms.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

PRE-MEETING RATIONALE

Biofilms are comprised of single or multiple species of microbial aggregates embedded in a self-produced matrix of extracellular polymeric substances. Regardless of the bacterial species, biofilm formation proceeds in known and well-defined steps. The first step or stage, adhesion, begins when bacteria sense and attach to surface of a material. The second stage is accumulation, where bacteria aggregate to form a mature biofilm. The last stage is dispersion or detachment [1]. The duration of each of these steps in biofilm formation varies from nanoseconds to hours to weeks, depending on various factors such as size of inoculum, mechanism of colonization (direct perioperative inoculation, later direct colonization due to break of barrier, bacteremic spread), surface properties of the foreign material, bacterial strain and virulence, bacterial species, host immunity, prior antibiotic usage and environmental factors, etc. [2–10].

For example, *Pseudomonas aeruginosa* (*P. aeruginosa*) contains several genes that are turned on within 15 minutes of its attachment to a surface that can be a starting point of biofilm formation [3]. Kanno et al. developed full thickness wounds on the backs of rats and inoculated them with *P. aeruginosa* carrying the green fluorescent protein gene; they found that biofilms could develop within eight hours [4]. When *Staphylococcus aureus* (*S. aureus*) was inoculated onto animal wounds, researchers found the development of clusters of cells (characteristic of a biofilm) after 6-24 hours post inoculation [11,12]. Oliveria et al. evaluated the time course evolution of biofilm in mastitis isolates and found no significant difference between *S. aureus* and *Staphylococcus epidermidis*. In their study biofilm forming ability increased with incubation period for both species [5]. Hoffman et al. researched adhesion patterns of single bacterium *Caulobacter crescentus* on a glass surface in a microfluidic device. They showed the importance of pili for hastening bacterial adhesion. In their study, irreversible adhesion events were more frequent in wild-type cells (3.3 events/min) compared to pilus-minus mutant cells (0.2 events/min) [13].

Koseki et al. [6] evaluated the difference in early biofilm formation of polysaccharide intercellular adhesin (PIA)-positive *Staphylococcus epidermidis* on five types of biomaterials and found no significant difference in biofilm coverage rate at two to four hour incubation, but at six hours post incubation cobalt-chromium-molybdenum alloy (Co-Cr-Mo) had a significantly lower biofilm coverage rate than other materials like titanium alloy (Ti-6Al-4V), commercially pure titanium and stainless steel. In this study authors point out a similar degree of smoothness across materials as a reason for no significant difference between them initially (two to four hours). In this study average roughness (Ra) was less than 10 nm [6]. This is corroborated by the previous reports that bacterial adhesion is influenced by the threshold of surface roughness at values more than 200 nm [14,15].

Some evidence suggests that bioactive substances such as hydroxyapatite may be more prone to bacterial adhesion than bioinert metals, such as titanium alloys and stainless steel [7]. Further studies have demonstrated that polymethyl methacrylate (PMMA) is capable of hosting biofilms that can cause acute, chronic and delayed-onset infections [8,9].

Biofilm adherence to biological or synthetic materials and foreign cells and resistance to antimicrobials are poorly understood. As biofilm formation can proceed through different pathways and time ranges, its detection may differ according to the time of observation. Investigational models to determine how environmental factors, such as surface geometry, physical and chemical characteristics, and local blood flow and immune system affect biofilm development on prosthetic joints are essential to further understand various bacterial biofilms and provide insight to therapeutic strategies.

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QUESTION 5: Do bacteria form biofilm on the surface of cement spacer in a similar fashion to a metallic implant?

RESPONSE: Yes. While the vast majority of studies have been in vitro, there is clinical evidence that majority of bacteria are able to form biofilm on the surface of cement spacer.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

PRE-MEETING RATIONALE

The majority of data assessing biofilm growth on polymeric materials and smooth surfaces has been collected from in vitro experiments [1]. As a general outline, microbial adherence to materials occurs in the following order: latex > silicone > PVC > Teflon > polyurethane > stainless steel > titanium [1,2]. This hierarchy of materials to bacterial adherence suggests that biofilms may develop more readily on polymer-based versus metallic material surfaces. Roughness may play a role in this [3]. However, time is also an important factor to consider. Verran et al. showed that *Candida albicans* adhered to a greater degree on roughened surfaces compared to smooth [4]. In their experiment, polymeric samples were incubated for one hour, and then assessed for adhesion profiles. Similar work was performed by Taylor et al. on cobalt-chrome materials with the same conclusion [5]. Although a one-hour incubation period may be beneficial to determine initial adherence profiles, it would be difficult to compare test criteria such as these to clinical scenarios where implanted materials are present for days, weeks, months or years. Wolcott et al. have shown that time may play an important role in biofilm maturation and antibiotic tolerance [6]. Biofilms are well-known to condition surfaces and make them conducive to their growth requirements [3]. Perhaps one of the most well-known examples of this is *Streptococcus mutans*, which conditions the enamel surface that allows adherence for hundreds of other bacterial species [7]. Given enough time, biofilms may flourish on surfaces in many environments and on surfaces that may otherwise be considered less culturable [3,8,9]. In-house experiments that are in process of publication have shown that even amongst the same species, varying strains can differ in rates of biofilm formation on titanium surfaces, but over time degree of biofilm formation is similar in bench-top conditions.

The principles and problem of biofilm formation apply to bone cement and metallic surfaces used in orthopaedic applications. Biofilms have been shown to develop on both material types and adversely affect clinical outcomes [10–13]. A seminal paper published by Gristina et al. provided one of the first indications of biofilm growth on an implanted metallic implant that was found to contribute to biofilm-related infection [14]. More recently, Stoodley et al. directly observed biofilms on antibiotic-loaded bone cement associated with an infected total elbow arthroplasty [12]. McConoughey et al. have also identified bacterial biofilms on implanted components [15]. Shaw et al. observed biofilm, via methylene blue staining, that had developed on a tibial tray and other total joint components during revision surgery [16]. In multiple cases, biofilm has been observed directly on clinical samples. Due to the heterogeneous and at times difficult nature of collecting clinical samples, more highly controlled, albeit confirmatory outcomes of biofilm growth on metallic and cement materials have been obtained from in vitro and in vivo experiments.

Minelli et al. showed the ability of multiple staphylococcal bacterial strains to form biofilm on bone cement samples in all cases [17]. Neut et al. observed that slime-producing *Pseudomonas aeruginosa* can readily form biofilm on cement material, and in the biofilm phenotype it may be more tolerant to antibiotics loaded in cement than planktonic bacteria [18]. Ensing et al. assessed biofilm growth on cement material and the potential of ultrasound to remove its presence [19]. More recently in a study by Ma et al., polymethylmacrylate spacers that were removed at the time of reimplantation following treatment of infected total knee arthroplasty were shown to have high levels of bacterial DNA despite extended exposure to antibiotics [20]. Biofilm formation on metal surfaces is also well-documented [21–24]. Nishitani et al. have also observed growth of biofilms on metallic implants in mice [25]. Williams et al. have shown that over multiple days of growth in a CDC Biofilm Reactor, polymicrobial biofilms of methicillin-resistant *Staphylococcus aureus* and *Bacillus subtilis* grow similarly on smooth or rough titanium surfaces [26].

In summary, indications that biofilm forms on bone cement and metallic surfaces in a similar fashion are present from clinical samples as well as in vitro and in vivo animal studies. There are indications that bacterial cells may adhere to and form biofilms more quickly on rough/porous materials, but over time bacteria may condition material surfaces that are smoother in nature such as metal and allow biofilm to form to a similar degree.

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QUESTION 6: Does *Mycobacterium tuberculosis* (*M. tuberculosis*) form a biofilm on implants?

RESPONSE/RECOMMENDATION: Few data from experimental in vitro and in vivo studies and a limited number of case reports indicate that *M. tuberculosis* has a slow, albeit significant, ability to form biofilm on metal surfaces. The group suggests that management of *M. tuberculosis* implant-related infections should be treated using the same principles as that of other implant-related infections.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

PRE-MEETING RATIONALE

Methods

A search of the English language literature on the question published during the period 1966–May 20, 2018 was conducted. The search strategy in PubMed used the terms *M. tuberculosis* and biofilm and identified 177 articles. All articles were reviewed for the response to the question. The vast majority of articles were categorized as basic sciences articles focusing on the components for tubercular biofilm formation in vitro. A systematic review to answer the provided question is not meaningful. Hence, the response of the question is answered as a summary of a narrative review.

Narrative Literature Review and Discussion

It is important to differentiate between *M. tuberculosis* and non-tuberculous mycobacterium. This review focusses only *M. tuberculosis*.

M. Tuberculosis Forms Biofilms

In the laboratory, *M. tuberculosis* shows peculiar aggregated growth, or in other words, can form organized pellicle-like structures [1]. The hallmark of biofilms is the self-production of the extracellular polymeric substance that holds the mycobacterial community together and confers phenotypic heterogeneity to

TABLE 1. Clinical data – PJI due to *Mycobacterium tuberculosis* treated antitubercular agents without surgery

Author/Year	Joint	Age/ Gender	Reported Risk Factors or Previous Clinical Hx	Preprosthetic Dx	Time Elapsed from Arthroplasty to Joint Infection	Time Elapsed from Joint Infection to Dx or Medical Therapy	Concomit-tant Infec-tions	Instrumental Examina-tions	Histological Examinations	Micro-biological Dx	Other Sites	Medical Therapy (Duration in Months)	Surgery	Time Elapsed from Start of Medical Therapy to Surgery	Follow-up from end of Therapy
Wray;1987	Knee	63/M	None	Osteoarthrosis	Postoperatively	NR	NR	Rx	Chronic granulomatous inflammation	NR	Lung	INH, RIF (12)	None	NR	18 months
Present work, case 2	Knee	62/M	None	Osteoarthrosis	Postoperatively	3 years	NR	Rx, Scint	Chronic granulomatous inflammation	Arthrocentesis cultures	None	INH, RIF (18), PZA (2)	None	NR	1 month
Tekin Koruk;2013	Knee	55/M	None	Osteoarthrosis	15 days	1 month	NR	Rx	Chronic granulomatous inflammation	Arthrocentesis microscopy and cultures	None	INH, RIF (12), PZA, EMB (2)	None	NR	NR
Kadakia; 2007	Knee	85/F	None	Traumatic fracture	1 month	3 months	Coagulase-negative Staphy-lococci	Rx	NR	Arthrocentesis cultures	Lung	INH, RIF, PZA, EMB (6)	None	NR	NR
Cansu;2011	Hip	46/F	None	Dislocation	4 months	NR	NR	Rx, CT	NR	Arthrocentesis cultures	None	INH, RIF, EMB (16), PZA (3)	None	NR	72 months
Marshall; 2007	Knee	48/M	AIDS	Osteoarthritis	6 months	3 months	NR	Rx, MRI	NR	Arthrocentesis microscopy, PCR and cultures	Lung, CNS	INH, PZA, EMB (1), MOX (1/2), RIF (1/2)	None	NR	Died during therapy
Present work, case 1	Knee	34/F	None	Rheumatoid arthritis	8 months	4 years	NR	Rx, MRI, LLS, PET	Chronic inflammation	Arthrocentesis cultures	None	INH, RIF (18), PZA, EMB (2)	None	NR	24 monhts
Jhoson;1979	Hip	51/F	Hip TB 41 yrs ago	Osteoarthritis consequent TB	13 months	NR	S. albus	Rx	NR	Arthrocentesis cultures	None	INH, RIF, EMB (on therapy)	None	NR	On therapy when published
Shanbhag; 2007	Hip	59/F	None	Osteoarthritis	14 months	2 months	Staphy-lococci	Rx, MRI	Chronic granulomatous inflammation	Arthrocentesis cultures	None	RIF, PZA, EMB (12)	None	NR	18 months
De Nardo;2012	Hip	67/F	None	NR	16 months	3 months	NR	CT, LLC	Chronic active inflammation	Arthrocentensis PCR	Psoas muscle, adrenals	INH, RIF (on therapy), PZA, EMB (3)	None	NR	On therapy when published
Lee;2012	Hip	62/M	None	Fracture	8 years	NR	NR	Rx, US, CT	Chronic active inflammation	Intraoperative microscopy and cultures	None	INH, RIF, PZA, EMB (6)	None	NR	24 months
Neogi;2009	Knee	73/F	None	Osteoarthritis	14 years	2 months	NR	Rx	Chronic granulomatous inflammation	Arthrocentesis PCR	None	INH, RIF (18), PZA (7), EMB (4)	None	NR	36 months
Egues Dubuc;2014	Knee	77/F	Anti-TNF therapy	Rheumatoid arthritis	NR	1 year	NR	US, Scint	NR	Arthrocentesis PCR	Lung, small intestine	INH, RIF, PZA (on therapy)	None	NR	On therapy when published

the genotypically identical cells [2]. Several studies have highlighted extracellular components within *M. tuberculosis* aggregation, including mycolic acids [3], complex sugars [4], cellulose, proteins, lipids and DNA [5,6]. In addition, *M. tuberculosis* residing within organized pellicle-like structures exhibits drug tolerance to antitubercular agents [3]. Thus, criteria of a structure to what is interpreted as biofilms are given.

M. Tuberculosis Biofilms in Humans

The clinical role of *M. tuberculosis* biofilms in humans is not fully understood. Basaraba and Ojha [7] provide convincing arguments that extracellular *M. tuberculosis* in necrotizing lesions likely grows as biofilms. Hence, mycobacterial biofilms may participate in the process of caseous necrosis and cavitation formation in lung tissue [5–7].

M. Tuberculosis Biofilms on Metal Surface

The vast majority of studies investigating *M. tuberculosis* biofilms uses polystyrene plates [8]. Ha et al. [9] compared the adherence and the biofilm formation of *Staphylococcus epidermidis* (*S. epidermidis*) with those of *M. tuberculosis* on four types of metal segments. In contrast to *S. epidermidis*, *M. tuberculosis* rarely adhered to metal surfaces and showed discrete biofilm formation. Similar results were reported by Chen et al. [10] who compared *S. aureus* and *M. tuberculosis* in vitro and in vivo. Adetunji et al. [11] analyzed *M. tuberculosis* biofilm formations on cement, ceramic or stainless steel coupons. The experimental settings in this study are difficult to transfer in an in-vivo implant model (e.g., more biofilms were formed when media containing 5% liver extract was used). However, more biofilms were formed on cement than on ceramic and stainless steel coupons [11]. Taken together, the few available data from in-vitro and in-vivo studies indicate that biofilm formation of *M. tuberculosis* on metal segments is poor in comparison to Staphylococcus spp.

Among the 66 cases reported by Veloci et al. [12], 13 (19.6%) were treated with antitubercular agents only. Hence, in these cases no surgical intervention was performed to reduce the mycobacterial load or to remove mechanically the biofilm adhering to the implant. One patient died because of far-advanced tuberculous meningitis, miliary tuberculosis of the lungs, femoral osteomyelitis and extended cold abscesses along the femoral shaft [13]. In the other cases, no failure was reported. Though only in 6 (50%) of 12 cases, follow-up results of ≥18 months after the end of therapy was available. Treatment duration ranged from 6 to 18 months. These data indicate that tubercular biofilm eradication is possible with chemotherapy only. Whether this is due to poor biofilm formation on metal implants or due to effective anti-biofilm activity of antitubercular agents cannot be assessed.

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QUESTION 7: What is the role of the microbial synergy in polymicrobial infections?

RESPONSE: In polymicrobial infections, a complex environment may be formed in which microbiological interactions exist between microorganisms. Scientific evidence exists to show that combinations of bacterial species may exist whereby these can protect each other from antibiotic action via the exchange of virulence and antibiotic resistance genes, and this may be evident in adverse outcomes for polymicrobial orthopaedic implant-related infections. It is also probable that polymicrobial infections may be more likely in patients with poor immunity and tissue healing.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

PRE-MEETING RATIONALE

Varying incidences for polymicrobial infections have been reported with rates ranging from 6% to 37% [1–5]. The literature consistently demonstrates that patients with a polymicrobial infection demonstrate inferior treatment outcomes. Tan et al. reported that patients with polymicrobial periprosthetic joint infection (PJI) had a higher failure rate (50.5%) compared with monomicrobial PJI (31.5%) and a higher rate of amputation (odds ratio [OR] 3.80), arthrodesis (OR 11.06), and mortality (OR 7.88) [2]. Similarly, Wimmer et al. demon-

strated that the infection free rate after two years was 67.6% for polymicrobial infections vs. 87.5% for monomicrobial infections in a series of 77 polymicrobial PJIs [6]. In addition, Marculescu et al. demonstrated that the 2-year cumulative probability of success of polymicrobial PJIs was 63.8% compared to 72.8% for monomicrobial PJIs [7].

There are several explanations for the increased rate of failure in patients with polymicrobial PJI. Some explanations of polymicrobial infection include the following: the association with a sinus tract or a soft tissue defect; the frequent presence with difficult to treat organisms, such as Enterococcus spp and gram negatives [2,7,8]; increased comorbidities [2,7]; and microbial synergy.

Microbial synergy is defined as an interaction of two or more microbes in an infection site that results in enhanced disease by creating a more favorable condition for one another, compared to infections containing a single organism [9,10]. According to this definition, it can be appreciated that polymicrobial infection have less optimal outcome over that of monomicrobial infections because of the enhanced pathogen persistence in the infection site, increased disease severity and antimicrobial resistance [10,11]. While microbial synergy results in an enhancement of the disease, real experimental data supporting this phenomenon is still limited [12–14], which may be attributed to the complex and dynamic web of interactions that occur in natural systems [15].

Identified types of polymicrobial infections are due to: (1) changes in relative composition of individual species of microbiota [16]; (2) colonization of a pathogenic microbe of an infection site that already contains commensal microbes; and (3) colonization of a pathogenic microbe on a body they don't usually habit [17].

Several mechanisms of microbial synergy have been proposed in order to explain microorganisms interactions during polymicrobial infections: (1) metabolite cross-feeding: reported as the consumption of metabolic end-products by one of the microbial communities involved and optimization of local environment with the metabolic end-products [9,18,19]; (2) dedicated signaling systems: capacity of many microorganisms to communicate and coordinate activities as a group through low molecular weight signals, called "quorum sensing" [20]; (3) stimulation of resistance to the immune system: production of chemical substances that induce resistance to immune system like outer membrane proteins that inhibits immune pathways [9,18]; (4) suppression of the immune system by commensal bacteria: promotion of growth environment for commensal pathogens [9,21,22]; (5) direct contact: formation of biofilm by membrane-bound structures (adhesins) between microbes [23,24]; and (6) increased virulence of the organisms: production of substances that enhance the virulence of other bacteria [9].

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QUESTION 8: Is the mapping of biofilm to a particular component or anatomical location an important consideration in management of implant related infections?

RESPONSE: At present, mapping of biofilms is only possible in the laboratory, not in the clinical setting. Therefore, it is of unknown clinical importance in relation to management of implant-related infections.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

PRE-MEETING RATIONALE

Total joint replacement has become a vital tool for the treatment of end-stage osteoarthritis of the knee and hip and has the potential to substantially improve a patient's quality of life when successful. However, periprosthetic joint infection (PJI) is a dreaded complication of arthroplasty procedures that often results in expensive intravenous antibiotics, longer hospital stays and numerous negative effects related to patient morbidity [1]. Occurring at a rate of around 0.5-2% across all primary total joint procedures, these PJIs often involve bacteria growing in a composite of cellular and extracellular matrix material complex, known as biofilms [2,3]. The exact location or predilection of biofilm growth on specific prosthetic components or materials remains an important, albeit understudied, question. There is no evidence in the literature that has mapped biofilm formation to one specific material type or location or demonstrated mapping's importance in management of implant related infections.

Previous research examining the role of biofilms in PJI virulence is primarily focused on detection methods, imaging modalities and bacterial classification. While mapping to particular components is not commonly a primary focus, some work has examined patterns of bacterial formation that offer preliminary insight. Stoodley et al. [4] have shown that colored fluorescent proteins can be expressed to directly observe *Pseudomonas aeruginosa* biofilms on 316L stainless steel screws. Patchy development was noted on screw shafts and between the threads of several screws, with no significant pattern of development noted.

Confocal laser scanning microscopy has also been shown to aid in biofilm visualization on implant materials and surrounding tissue [5]; however, focused analysis does not exist regarding mapping or preferential formation of the biofilm on specific components or anatomic regions. Kobayashi et al. [6] and Nguyen et al. [7] have demonstrated the utility of ultra-sonication in detection of biofilms in PJI cases, showing that brief exposure of one to five minutes of infected components to ultra-sonication is effective in detecting bacterial adherence. However, few components were shown to harbor bacteria and those that did were not examined for anatomic or component-specific variability. Preliminary work by Gómez-Barrena et al. [8] showed no significant difference between hip and knee components in harboring bacterial biofilm formation. While this work focused primarily on the pathogenesis of various microorganisms and only classified components as "hip" or "knee," the finding that component type did not affect adherence shows primary indications that mapping biofilm formation may not be important to the management of PJIs. Existing research regarding biofilm mapping is not complete and cannot definitely define the importance of its practice. There is a need for additional work to replicate preliminary experiments and directly study the location of biofilm formation on orthopaedic components.

Another aspect of mapping to be considered is the material composition of orthopaedic components and the possible varying ability of such materials to harbor biofilm formation. Sheehan et al. compared stainless steel and titanium components using isolated strains of *Staphylococcus aureus* and *Staphylococcus epidermidis* in a femoral intramedullary implantation model in rabbits [9]. This study demonstrated higher levels of biofilm adherence to stainless steel components within the first 48 hours. Both strains showed this preferential growth, with higher levels of adherence reaching nearly 150% on stainless steel compared to titanium. Tuke et al. expanded the analysis of implant failure to analyze the potential role of metal-on-metal bearing surfaces [10]. A wear patch was noted to form on retrieved failed devices, indicating a potential loosening of the orthopaedic components and opportunity for colonization. These studies demonstrate the possibility of material-specific variation in biofilm formation that may allow for mapping. It appears possible that specific components, due to their composition or anatomical position, may be more susceptible to bacterial colonization with strains associated with PJI. However, there is a lack of evidence regarding materials commonly used in implant devices, with only preliminary and speculative data suggesting variation that may lead to improved surgical management.

Given the limited number of studies evaluating the location of biofilms on specific components isolated from PJI patients, either clinically or in the laboratory, we conclude that there is no strong evidence that biofilm formation favors either a specific location or material type in total joint arthroplasty. Anecdotally, it seems intuitive that knowledge of biofilm location would aid in surgical therapy, and a recent paper argues that an orthopaedic biofilm disclosing solution used intraoperatively would be a useful surgical tool [11]. However, the lack of evidence in the literature prevents the conclusion that mapping biofilms to a particular component is of clinical relevance.

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Disruption

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QUESTION 1: Is there evidence that interference with bacterial communication by blocking quorum sensing molecules can minimize biofilm formation in vivo?

RESPONSE: In vivo animal studies have demonstrated that interference with quorum sensing signals/molecules in some infections leads to decreased biofilm formation. There are contradictory results in *Staphylococcus* species. However, there are no clinical studies demonstrating this phenomenon.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

PRE-MEETING RATIONALE

While there is extensive in vitro and in silica work being done and reported on quorum sensing and anti-quorum sensing molecules, otherwise known as quorum quenching, there are limited in vivo data and none of the anti-quorum sensing strategies are ready for widespread clinical application. Based on a search of the NCBI, Embase and Scopus databases, there are seven in vivo investigations that were reported during the last five years [1–7] (Table 1). In addition, there have been reports of quorum sensing inhibitor

TABLE 1. Seven in vivo studies over the last five years

Study #	Animal Model	Agent	Mechanism	Clinical Effect
1 [1]	Medaka fish peritoneal catheter infection	3-Phenyllactic Acid (PLA)	Antagonistically binds to quorum sensing receptors RhIR and RqsR, blocking initial attachment of Pseudomonas aeruginosa (PAo1) thereby delaying biofilm formation [1]	Decreased biofilm formation
2 [7]	Wistar rat pyelonephritis	phytol	Down regulate offimA, fimC, flhC, flhD, bsmB, pigP shlA genes in S. marcescens leading to decreased biofilm formation and virulence factor production	Decreased bacterial counts and virulence enzymes (lipase and protease) decreased inflammatory markers (MDA, NO, MPO) and histologically no acute inflammation
3 [2]	Mouse gingivitis	Quorum Sensing Inhibitors (furane compunds, d-ribose)	Interfere with AutoInducer-2	Decreased colony counts and alveolar bone loss
4 [4]	Round worm survival (Caenorhabditis elegans)	Sub-inhibitory concentration of ceftazidime	Inhibition of QS regulated virulence traits and biofilm formation; binds to the las and pqs QS receptors in P. aeruginosa	Increased survival
5 [5]		Acylase	Degrades Quorum sensing peptides	Delay biofilm formation for S. aureus and P. aeruginosa for up to 7 days
6 [6]	Larval oyster mortality	Phaeobacter gallaeciensis S4Sm	Down regulate pathogen virulence genes	Decreased mortality from V. tubiashii infection
7 [3]	Round worm survival (Caenorhabditis elegans)	Pyrrolo (1,2-a) pyrazine-1,4-dione, hexahydro-3-(2-methylpropyl) from Alcaligenes faecalis	Modulate expression of quorum sensing (QS) regulators luxT and lafK	Increased survival from V. alginolyticus infection

and quorum quenching studies presented at scientific meetings utilizing multiple in vivo models [8].

The experimental strategy varies. In vitro data are relied upon to identify the molecular mechanism leading to interference with quorum sensing that causes decreased biofilm formation, whether it be blocking the signaling peptide production, blocking receptors or active initiation an antagonist signals by the agent. The in vivo data confirm that the agent decreases biofilm formation.

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QUESTION 2: Can a biomaterial surface be modified to dispel bacterial adherence and biofilms? What are the potential concerns in modifying implant surfaces to combat biofilms?

RESPONSE: The purpose of the surface modification is to decrease perioperative bacterial adherence and thus prevent biofilm formation. This has been shown in in vitro studies and in vivo animal models. There have been numerous strategies devised to alter surfaces. Such modified surfaces may interfere with the expected osseointegration, mechanical stability and long-term implant survivability. The duration of long-term anti-infective effects are unknown. To date, no positive in vitro effect has been translated into a clinical setting.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

PRE-MEETING RATIONALE

Periprosthetic joint infections (PJI) represent 1-20% of the failure mechanisms in total joint arthroplasty leading to significant morbidity and mortality [1–3]. The material surface used for implantation is a significant factor in bacterial colonization leading to PJI [4,5]. Some surfaces are more prone to bacterial adherence and formation of biofilms. A biofilm is an aggregate of microbial cells that are irreversibly associated with a surface and encapsulated in a complex polysaccharide "slime" extracellular matrix that may include enzymes, crystals and glycoproteins - together forming a living tissue [6,7]. The most common microorganisms residing in biofilms are *Staphylococcus S.* species [8,9]. The bacteria in biofilms take either sessile forms on metal, bone fragments and cement; or planktonic forms that can disperse as clumps within the joint fluid [10,11]. Due to such complexity of form, material and function, the question remains whether modified implant surfaces can play an anti-infective role and what are the main concerns with modifying biomedical devices.

Can a Biomaterial Surface Be Modified to Dispel Bacterial Adherence and Biofilm?

In 1987, Anthony Gristina [12] was the first to propose the concept of a race for the surface, wherein the fate of the biomaterial implant is dependent on a balance between tissue integration and microbial adhesion with biofilm formation. This concept sets the hypothesis that material modifications that improve osseointegraion while inhibiting bacterial adhesion would provide a theoretical advantage and eliminate the risk of infection [13]. As a result, there is a wide array of anti-infective surfaces proposed for utilization in orthopaedic implant applications.

Gallo et al. [14] summarized the available options as bactericidal, anti-adhesion surfaces, multifunctional/smart coatings and alternative materials.

Romanò et al. [15] propose a newer classification regime that describes antibacterial coating under three distinctive groups [1]:

1. *Passive surface finishing/modification* Surfaces that prevent adhesion without releasing anti-bacterial substances.
2. *Active surface finishing/modification* Surfaces that release anti-bacterial substances.
3. *Perioperative antibacterial carriers or coatings* Carriers or coatings applied during surgery that are antibacterial and either biodegradable or non-biodegradable.

Active surfaces and perioperative coatings provide only temporary solutions while they exhaust their antimicrobials in time. Passive surfaces may not provide the necessary bactericidal properties needed to eliminate the infection while their action is limited to the immediate peri-implant area. The ideal implant surface should have: (1) a strong anti-infective potential, (2) long duration of effect, (3) biocompatibility with mechanical construct and stability and (4) minimal host response and harm [16–18]. To achieve that, surfaces

TABLE 1. Proposed anti-infective surfaces for utilization in orthopaedic implant applications

Method	Type	Examples
Bactericidal	Inorganic	Ag, AgNP, AuNP, TiO2, Se, CuNP
	Organic	Coated or covalently linked antibiotics, chitosan derivatives
	Combined	Multilayer coating, positively charged polymers
	Other	Non-antibiotic (peptides, enzymes, oils)
Anti-adhesion		Anti-adhesive polymers
Multifunctional/smart coating	Passive	Nanostructured "smart" materials
	Active	Sensors conjoined to nanocontainers
Alternatives		Lytic bacteriophages

Ag, silver; NP, nanoparticles; TiO2, titanium oxide; Se, selenium; Cu, copper

can be physically and mechanically prepared and coated or chemically modified.

The early reversible adhesion stage of bacteria to titanium is largely influenced by the topographical features on the surface [19]. Several anti-adherent coatings on titanium have been created by surface modification with polymers, copolymers or proteins. Del Curto et al. [20] has shown that the crystalline phase of titanium oxide on the surface of biomaterials reduced bacterial attachment without adverse effects on the biocompatibility. Ferraris et al. [21] showed that mechanically produced nanogrooves (0.1-0.2 um) and keratin nanofibers can increase biocompatibility without increasing bacterial adhesion. Lorenzetti et al. [19] has applied hydrothermic treatment methods to similarly achieve decreased bacterial adhesion. This data is very encouraging and supports the concept that biomaterial surfaces can be modified to dispel bacterial adherence.

Silver (Ag) has been known throughout history not only for its jewelry applications but for its antimicrobial effects [22,23]. The mechanism of action is thought to be the formation of reactive oxygen species and biologically active ions that damage bacterial walls and bind to nucleic acids and interrupt bacterial replication [24]. An added advantage of Ag usage is the effect against surface-adhered bacteria without significant drug-resistance [25,26]. Harrasser et al. [27] studied the antimicrobial effects of Ag and has observed significant antimicrobial activity that was positively correlated with Ag concentrations. A recent study by Aurore et al. [28] indicated that Ag nanoparticles (AgNPs) enhanced the bactericidal activity in osteoclasts.

As such, AgNPs have gained attention for their application on implant surfaces due to their anti-biofilm potential, wide-spectrum antimicrobial properties and low cytotoxicity to human cells [18,22,29–33]. There is an abundance of literature that examine the anti-biofilm effect of AgNPs [18,25,34]. Kalishwaralal et al. [35] demonstrated that AgNPs at a concentration of 100 nM almost entirely inhibited biofilm formation (> 95%) from *S. epidermidis* and *Pseudomonas aeruginosa*. Slane et al. [33] found that bone cements impregnated with AgNPs significantly reduced biofilm formation compared to standard cement. Some studies have also mentioned the synergistic effect of AgNPs with antibiotics [36–38]. The most notable advantage of AgNP-coated surfaces is the ability to exhibit a continuously controlled-release of active agents to the periprosthetic region for a substantial period of time, thus working at both the surface layer but also in the immediate environment.

Recently, iodine has been shown to be a successful adjuvant for irrigation and debridement in cases of PJI [39]. Adapting this idea to implant surfacers, Tsuchiya et al. [40] report on a clinical study of more than 222 patients in whom iodine surface treated implants were very effective for preventing and treating infections after orthopaedic surgery. No clear cytotoxicity or adverse effects were observed. Shirai et al. [41] similarly demonstrated a significant reduction in pin tract infection rate by using iodine surface-treated insertion pins and external fixators. Kabata et al. [42] also show that iodine treated hip implants remained free of infection in 14 revision cases for infection and in 16 immunosuppressed primary total hip arthroplasties. No issues related to local and systemic toxicity or impaired osteoconductivity and bone bonding have been reported in any of these studies.

Similar to Ag and iodine, multiple studies have targeted incorporation of antibiotics into surface coatings directly deposited onto the implant [43–45]. Most of these applications build on the information learned from antibiotic-laden bone cements and provide an initial protective barrier for infection [46–48]. Current protocols include hydrogels, poly-D, L-lactide, calcium phosphate or carbonated hydroxyapatite antibiotic coatings. Other direct techniques attempt to physically modify the surface for antibiotic adsorption, or simply dip the implant in antibiotics producing a transient coating [48–50]. Recent scientific progress in biomolecular interactions and nanoscale engineering provides new inspiration for medical implant designs that may have the potential to deal with infection [51,52]. Antibiotics covalently linked to metallic surfaces have been shown to inhibit bacterial colonization both in vitro and in vivo [13,53,54]. Despite all progress, most systems are rudimentary and difficult to scale up to industry standards; further research and a smarter implant technology is necessary. Such technology should directly integrate biological defenses in the implant design, making protection feasible for the life of the replacement prosthesis.

What Are the Main Problems in Modifying Implant Surfaces in the Fight Against Biofilms?

One of the main concerns of antimicrobial biomaterials is the possible cytotoxic effect of the surface modification as related to osseointegration and implant survival in vivo. Based on a preliminary literature review, only four laboratory studies [55–58] and one clinical study [59] reported the side effects of surface modification. Ag surface modifications have shown higher lactate dehydrogenase (LDH) activity as a marker of cell death, as well as lower cell count and alkaline phosphatase (ALP) activity [55–58]. Nevertheless, such

effects are hard to correlate with clinical outcomes. Glehr et al. [59] performed the only clinical study that focused on Ag while examining its use in mega-prosthesis. They have documented the presence of heavy metal poisoning symptoms, even though no correlation with the blood Ag concentration was observed. Another two in vitro studies used zinc and farnesol (anti-fungi medicine) surface modifications respectively. The results showed lower ALP activity as well as pre-osteoblastic cell damage. Multiple studies thus agree that AgNPs have the potential to be toxic to many cell types in a dose- and time-dependent manner, especially when inhaled, injected or ingested [60–62]. Interestingly, Shen et al. [63] conducted a study which revealed that both cobalt chrome alloys and pure titanium had cytotoxic effects to osteogenic precursor cells and mesenchymal stem cells, while the incorporation of AgNPs reduced this cytotoxicity.

When working with modified surfaces, bacteria can ultimately adapt and develop resistance to the agent used. Antibiotic resistance is an everyday occurrence in clinical practice. Bacteria have also been shown to surmount resistance to the ionic form of Ag, and less commonly, to AgNPs [64,65]. This is because prolonged exposure to AgNPs, unlike Ag ions, is less likely to result in resistance genes, since AgNPs have broad-spectrum capabilities by targeting multiple sites on or within bacterial cells [66]. Nevertheless, resistance to silver seems to be a slow process and is a less of a problem compared to antibiotic resistance [67]. Concerning though, Kaweeteerawat et al. [68] suggest that AgNPs could potentially enhance bacterial resistance to antibiotics through promoting stress tolerance by induction of intracellular reactive oxygen species causing DNA mutations.

In conclusion, bacterial biofilms are difficult for antimicrobial agents to penetrate. Preventing biofilms and bacterial adherence is probably the only effective way to address the problem of PJI. AgNPs and iodine are gaining increasing popularity especially for their anti-adhesion, anti-infective, and minimal bacterial resistance properties. Nevertheless, further investigation of the long-term outcomes of patients with modified surfaced implants is warranted.

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QUESTION 3: What is the relevance of minimum inhibitory concentration (MIC) of infecting organisms in biofilm-mediated chronic infection?

RESPONSE: The use of MIC is limited to (1) defining antibiotics that the microorganism is susceptible to in its planktonic state but cannot be used to guide treatment of biofilm-based bacteria and (2) selecting long-term suppressive antibiotic regimens where eradication of infection is not anticipated. Alternative measures of antibiotic efficacy specifically in the context of biofilm-associated infection should be developed and validated.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

PRE-MEETING RATIONALE

MICs are used to define an individual microorganism's (hereafter limited to bacteria) susceptibility to a distinct array of antibiotics. Established methodologies for determining MICs relate to the planktonic state of the bacteria but not to biofilm-indwelling bacteria [1].

The majority of information relating to susceptibility testing and biofilm-indwelling bacteria originates from research in Cystic Fibrosis [2]. In relation to implant-associated biofilm infections, central venous catheters and urinary tract catheters are often investigated, but little clinical research has been performed in orthopaedic implant-associated biofilm infections [2,3].

As early as 1990, Anwar and Costerton identified the need for an extreme increase in in vitro concentrations of antibiotics, to which the planktonic bacteria were fully susceptible, when treating biofilm-indwelling bacteria [4,5]. In a review by key-opinion leaders on the topic of antimicrobial susceptibility testing in biofilm-indwelling

bacteria, it was noted that MIC is not suitable in predicting the effect of an antibiotic for a biofilm infection [6]. In the 2014 European Society for Clinical Microbiology and Infectious Diseases guidelines for the diagnosis and treatment of biofilms infections, it is noted that antibiotic susceptibility determination by MIC offers no guide to clinicians in the treatment of biofilms [7]. Rather than MICs, clinicians may need to rely on other measures of antibiotic efficacy, such as minimum biofilm eradication concentration (MBEC), minimum biofilm bactericidal concentration (MBBC) or minimum biofilm inhibitory concentration (MBIC). These are likely to be 100-1000 times the MIC, but the associated breakpoints that would permit reliable prediction of treatment success have not yet been established.

Theoretical mechanisms driving the high-level of resistance to antibiotics in biofilm include both the mechanical exclusion of antibiotic molecules by the polysaccharide matrix and the presence of dormant persister organisms within the biofilm. The relative contribution of each of these mechanisms is uncertain, but emerging data suggest that persister organisms constitute up to 10% of biofilm. Due to the adapted phenotype, they are able to evade the antimicrobial action of a variety of conventional antibiotics that rely on disruption of cell processes for their efficacy. Post et al. showed that, although it was possible to eradicate biofilm caused by *Staphylococcus aureus* (*S. aureus*), the necessary time-concentration profile could not be achieved in vivo by systemic administration or by any local delivery vehicles currently available [8]. Urish et al. concluded that tolerance was primarily a phenotypic phenomenon as increasing cefazolin exposure did not result in changes in MIC [9].

In two studies, Antunes et al. identified that among biofilm-indwelling Staphylococcus species isolates, 89% were considered to be clinical resistant to vancomycin, even when the same isolates all presented MIC values categorizing the isolates as fully susceptible to vancomycin (MIC </= 2μg/mL) [10,11]. The authors concluded that this particular observation showed "that biofilm production results in an important barrier to antimicrobial diffusion into the biofilm" and that "antimicrobial susceptibility testing based on MIC values alone cannot accurately determine the exact susceptibility of bacterial biofilms."

Ray et al. tested ceftriaxone and gentamicin, both commonly used antibiotics in orthopaedic surgery, against *Serratia marcescens* biofilm in vitro at doses of 10, 100, 1,000 times that of the established MIC for the planktonic isolate and found that the antibiotic, even at these concentrations, did not reduce biofilm biomass [12].

Reiter et al. tested rifampicin and vancomycin against methicillin-resistant *S. aureus* planktonic and biofilm isolates in vitro and found 32-32,000 times increase in resistance for rifampicin and 8-512 times increase in resistance for vancomycin in biofilm isolates [13]. They subsequently concluded that the tested antibiotic were not able to eradicate mature biofilm at the concentrations needed for planktonic microbes (the MIC).

Ruppen et al. tested gentamicin as an adjuvant to penicillin in *Group B Streptococcus* biofilm in vitro, and found a 2,000-4,000 times increase in resistance for penicillin in the presence of biofilm and 1-4 times increase for gentamicin [14]. The authors noted that the gentamicin doses tested did not correlate with achievable in vivo concentrations. The authors concluded that the MIC did not correlate to the susceptibility to the tested biofilm strains.

Hajdu et al. tested an array of antibiotics against *Staphylococcus epidermidis* biofilm in vitro. The planktonic bacteria susceptibilities were tested to all antibiotics in the study. When biofilm-indwelling bacteria was tested, susceptibilities were up to 128-times the established MIC. Only ceftriaxone showed a minor reduction in total biofilm biomass. No eradication occurred for any antibiotics at any level above MIC; it was also noted that these levels were much higher than any clinical in vivo achievable concentration [15].

Ravn et al. tested dislodged biofilm from in vitro implant infections of *S. aureus*, *Staphylococcus epidermidis*, *Escherichia coli* and *Cutibacterium acnes* and found antimicrobial susceptibility to be identified at 4 times that of MIC (for *Escherichia coli* and ciprofloxacin) to 1.024 times that of MIC (for staphylococcus species + *Cutibacterium acnes* and vancomycin) [16]. The authors concluded that MIC correlation to in vivo values may not affect biofilm-indwelling bacteria.

Monzón et al. tested *Staphylococcus epidermidis* biofilm susceptibility on an array of antibiotics in vitro. All the isolates tested were fully susceptible to vancomycin in their planktonic form. The authors found that vancomycin, teicoplanin, clindamycin and oxifloxacin at MIC had a low killing rate in 24-hour mature biofilm. Rifampicin was not affected by the presence of mature biofilm and remained with a high killing rate at MIC [17]. The authors concluded that antibiotics may lose their killing ability in mature biofilm at clinical relevant in vivo levels, despite being fully susceptible at MIC.

Molina-Manso at el. tested susceptibility of Staphylococcus species biofilm in vitro and found that none of the tested antibiotics (including rifampicin, vancomycin, clindamycin, cloxacillin, ciprofloxacin) could eradicate the biofilm-indwelling bacteria, even at concentrations highly above the established MIC for the individual isolates [18].

Claessens et al. tested the effect of antibiotic concentration at up to 40 times the established MIC of the individual isolates in *Staphylococcus epidermidis* biofilm in vitro and found that only rifampicin could decrease but not eradicate the biofilm mass, whereas vancomycin, teicoplanin and oxacillin did not decrease the biofilm mass [19].

Given the plethora of evidence detailed above, there is a clear need to seek alternative approaches to the prevention and treatment of biofilm related infections. The use of local antibiotic delivery systems is widely regarded as a possible means to achieve sufficiently high concentrations of antibiotic to exceed the MBEC. However, there is little guidance on the optimal duration that MBEC should be exceeded to affect a cure. There is also concern that, although early elution of antibiotic from cement produces high local concentrations of antibiotics, late sub-MIC concentration may promote the development of antibiotic resistance, particularly amongst persister populations. Furthermore, the MBEC may well change with time of exposure to antimicrobials further complicating the determinants of optimal local dosage and carrier systems [20].

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QUESTION 4: What is the minimum biofilm eradication concentration (MBEC) of anti-infective agents?

RESPONSE/RECOMMENDATION: The MBEC of antimicrobial agents is a measure of in vitro antibiotic susceptibility of biofilm producing infective organisms. It is dependent on the surface, medium and the exposure period to an antimicrobial agent. There are no standardized measurement parameters for MBEC. MBEC is currently a research laboratory value and lacks clinical availability. In the group's opinion, there is value in developing a clinically-validated MBEC assay.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

PRE-MEETING RATIONALE

A Medline query on the item "minimum biofilm eradication concentration" retrieved 149 references. For the most part, these references relate to bacteria with little or no involvement in infection on orthopaedic devices. A query about "minimum biofilm eradication concentration of infective agents" retrieved 18 references; none of them clearly related to bone infection on material. The Medline request "minimum biofilm eradication concentration and implant associated infection" retrieves only three references [1–3].

The work of Coraça-Huber et al. [1] focuses on the evaluation of a study model of the minimum bacterial concentration (MBC) in infections on material, using strains of *Staphylococcus aureus (S. aureus)* and collection *Staphylococcus epidermidis (S. epidermids)*. Biofilm formation is supported by Innovotech, Inc.'s MBEC-HTP (high throughput plates) system (Edmonton, Alberta, Canada). The formation of biofilm is documented by electron microscopic study. The comparison of the minimum inhibitory concentration (MIC) and MBEC was made in this model for daptomycin, gentamicin, vancomycin, rifampicin, fosfomycin, clindamycin and linezolide. Biofilms generated by *S. epidermidis* show less resistance to antibiotics than those generated by *S. aureus*. The MBEC is much higher than the MIC of all antibiotics. Daptomycin and rifampicin are the most effective antibiotics against *S. aureus* embedded within a biofilm without obtaining their complete eradication.

Brady et al. [2] raised a question about the validity of the MBEC to replace the IJC in situations of infection on equipment. Twenty staphylococcal isolates from catheter infections were studied (17 CNS, 3 MSSA) and ten antibiotics were tested (penicillin, oxacillin, erythromycin, clindamycin, fucidine, tetracycline, gentamicin, vancomycin, teicoplanin and ciprofloxacin). The quantification of biofilm formation on microtiter plates and Tryptic Soy Broth (TSB) is obtained by crystal violet method. Detection of the biofilm formation mechanism (protein or polysaccharide) is obtained by treatment of sodium metaperiodate and protein kinase plates. The search for the ica operon (code in staphylococci for the production of enzymes necessary for adhesion) is done by polymerase chain reaction. Sixteen of the 20 strains (80%) tested produce biofilm; low for 8 strains, moderate for 2 strains, and high for 6 strains, all carriers of ica operons. The MBEC was 10 to 1,000 times higher than the MIC for bacteria producing biofilm. In practice, the MBC is > 256 µg/ml for all strains studied, whether or not biofilm production is proven by the techniques used, raising the question of strains forming a protein biofilm that cannot be quantified by the crystal violet method.

Zaborowska et al. [3] analyzed the sensitivity of staphylococci and enterococci from bone infections on material according to their biofilm production. The 13 strains studied were derived from infections on percutaneous bone anchoring material, on femoral amputation stumps for fitting. This technique involves a permanent protrusion of a titanium implant through the skin, a potential entry point for bacteria from the cutaneous and fecal flora. The bacteria studied were obtained from bone and material samples obtained from 11 infected patients. These are four strains of *S. aureus*, three strains of coagulase-negative staphylococci and six strains of *Enterococcus faecalis*. Ten antibiotics are tested in MIC and MBEC (clindamycin, gentamicin, vancomycin, linezolide, ciprofloxacin, oxacillin, fucidic acid, ampicillin, trimethoprim/sulfamethoxazole and rifampicin). The microtiter plate culture in TSB is used to evaluate the biofilm

production capacity of the bacteria analyzed. The total mass of the biofilm formed is measured by the crystal violet technique to determine a biofilm score (absent, low, moderate, high production). The production of exopolysaccharide (slime) is measured by the Congo red technique. The search for the ica operon for staphylococci is obtained by PCR test. The determination of the MBEC is obtained by the Calgary Biofilm Device (CBD). Eleven of the 13 strains studied produce biofilm, the quantity of biofilm is heterogeneous according to bacterial species. The MBEC is significantly higher than the MIC for the 10 antibiotics studied. The ratio MBEC/MIC is variable with marked differences between bacterial species. The MBEC is high and homogeneous for all strains of *Enterococcus faecalis*: MBEC/MIC from 64 to 2048, median 512, for vancomycin, ciprofloxacin, linezolide, ampicillin and rifampicin. In comparison, Staphylococcus strains show significant inter strain variability; for *S. aureus* MBEC/MIC ranges from 1 to 2048, median to 9, for the 10 antibiotics tested. For *S. epidermidis* the ratio ranges from 0.0038 to 64, median to 1. The ica operon is isolated for all staphylococci; however, two strains do not produce slime by referring to the Congo red technique, expressing variability in gene expression. For these two strains, the biofilm score assessed by the crystal violet method was strongly positive, indicating that this biofilm consisted mainly of aggregated cells without slime production.

The clinical follow-up of the 11 patients was correlated to the results expressed in MBEC. Failure was correlated with a high MBEC value without statistical evidence. Two patients did not present any complications (recurrence, reinfection or need for material removal). For one, the strain did not produce biofilm; for the other, biofilm production was low. For other strains with low to moderate biofilm production, patients experienced one or two complications. One patient developed all three complications and the infecting strain was highly biofilm producing.

Of these three studies, only Zaborowska et al.'s [3] corresponds to a clinical situation of infection on an orthopaedic device. As in the other two studies, the work presented here only tests antibiotics as monotherapy, whereas clinical use is readily with dual therapy, particularly when rifampicin is prescribed. The work of Saginur et al. [4] on 17 strains of *S. epidermidis*, 11 strains of methicillin-susceptible *Staphylococcus aureus* (MSSA) and 12 strains of methicillin-resistant *Staphylococcus aureus* (MRSA), isolated from infections on material tested in MIC and MBEC (CBD device) 9 antibiotics in monotherapy and 94 combinations of antibiotics in bi or tritherapy. The MBEC is significantly higher than the MIC, but a significant heterogeneity between strains is also found in monotherapy. Among the 94 antibiotic combinations tested, 11 are bactericidal on more than 90% of MSSA strains growing in biofilm and 9 are for *S. epidermidis*. Rifampicin is the antibiotic most often present in these combinations.

The efficacy of antibiotics against bacteria growing in a biofilm, is generally explored in vitro under standardized, brief conditions of exposure of the bacterial strain to the antibiotic tested. In clinical practice, exposure to antibiotics is prolonged [5]. In this work, bacterial strains (MSSA, MRSA, *S. epidermidis*, *E. coli*, *Pseudomonas aeruginosa*) are tested for growth in a biofilm at varying antibiotic concentrations for three antibiotic exposure durations of one, three and five days. For most strains and antibiotics tested, the MBEC is significantly lower after 5 days of exposure to antibiotics than that measured after 24 hours of exposure.

It is commonly accepted that bacterial adhesion and bacterial growth within a biofilm, are the determinants of infection on material. It is also commonly accepted that the effectiveness of antibiotics within a biofilm is greatly diminished. Measurement of in vitro antibiotic activity by the MIC determined on planktonic bacteria is not predictive of in vivo antibiotic activity on bacteria growing in a biofilm. The MBEC is the supposedly most appropriate parameter for predicting the efficacy of antibiotics in vivo. The literature review shows that this parameter is over the last few years increasingly studied and taken into account to test antibiotics or various molecules against multiple microorganisms.

While the in vitro MBEC determination method itself is not problematic, the measurement of biofilm production is more random. Biofilm is made up of both bacterial cells and a substance of either a polysaccharide (slime) or protein nature. Not all bacteria produce biofilm. For staphylococci, the production of biofilm is linked to the existence of an operon (ica), detectable by PCR but whose expression is variable, and the highlighting of the operon does not mean slime production. The measurement of the overall mass of biofilm, generally by the crystal violet technique, which potentially defines biofilm scores (absent, weak, moderate, strong), does not necessarily account for the composition of this biofilm, likely to modify the MBC of antibiotics.

The capacity to produce biofilm is heterogeneous depending on the bacterial species. On the available data, the capacity to produce biofilm is strong for *Enterococcus faecalis* without inter-strain variability. For staphylococci, the capacity to produce biofilm seems more marked in *Staphylococcus aureus* than in staphylococcus epidermidis, but inter-strain variability is important for staphylococci. Rifampicin appears to be a more active antibiotic in biofilm than average. However, the rule is by no means absolute. The efficacy of antibiotic combinations is significantly superior to that of monotherapy molecules.

In a clinical situation, for a given strain, the MBEC cannot be estimated a priori, at least for staphylococci. Of the few published data, the MBEC still appears to be higher than at least 64 times the MIC for antibiotics active against *Enterococcus fecalis* (ampicillin, vancomycin, linezolide, rifampicin). For other bacteria, the MBEC of active antibiotics is not known.

There is no antibiotic combination that guarantees bacterial eradication in the biofilm for a given strain of staphylococcus, although antibiotic combinations are generally more effective than monotherapy treatments. The in vitro measurement of the MBEC is not a routine use for the moment. The research field needs to define a standardized methodology for possible use in clinical practice. High biofilm production appears to correlate with a higher complication or failure rate than low or absent biofilm production without statistical demonstration at this time.

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QUESTION 5: Do bacteriophages have a role in treating multidrug-resistant periprosthetic joint infection (PJI)?

RESPONSE: Unknown. Although some preclinical and clinical studies have demonstrated a good safety profile as well as promising therapeutic effects using bacteriophages for treating bone and joint infections, further clinical research using bacteriophage therapy in patients with multidrug-resistant PJI is required.

There are known obstacles to bacteriophage therapy, including the fact that bacteriophages are neutralized in serum and relevant pathogens contain Clustered Regularly Interspaced Short Palindromic Repeats - associated protein-9 nuclease (CRISPR/cas9) immunity against bacteriophage. Phages are usually bacterial strain specific; thus, a cocktail of different bacteriophage lineages may be necessary to effectively treat biofilm-mediated infections.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

PRE-MEETING RATIONALE

PJI represent serious issues for patients worldwide. The surfaces of orthopaedic implants are all susceptible to colonization by biofilm-forming bacteria, such as methicillin-resistant *Staphylococcus aureus* (*S. aureus*) (MRSA), *Pseudomonas aeruginosa* (*P. aeruginosa*) and numerous other organisms, whose presence has been reported to play a key role in the occurrence of PJI, thus leading to antibiotic resistance [1–4]. To overcome these problems novel treatment strategies focusing on disrupting biofilms are being developed [5]. Utilization of lytic bacteriophages to eradicate bacteria causing biofilms is one of the promising emerging technologies [3,6].

Bacteriophages are natural viruses that infect bacteria. They are one of the most abundant organisms in the biosphere. Each bacteriophage is specific to a particular microbial species. Like all viruses, phages are only able to replicate inside their host cells. Lytic phages inject their genetic material into the host bacterial cell, cause bacterial cell lysis that liberates subsequent new phage particles. These new particles allow successive infection of additional bacteria in a rapid and exponential pattern, facilitating the complete eradication of the bacteria. The French microbiologist Felix d'Herelle first described bacteriophages in 1917 [7]. By their nature, bacteriophages are good candidates for antibacterial therapy. Indeed, they target a bacterium specifically, as long as the corresponding host bacteria is present. In comparison with antibiotics, this phenomenon is unique as it is exponential and self-sustained after a single or a few administrations. Moreover, lytic bacteriophages do not affect eukaryotic cells and not impact the gut microbiota when administered locally.

Bacteriophage technology is particularly promising in patients with multidrug-resistant PJI as: (i) multidrug-resistant PJI are becoming more and more frequent [8,9]; (ii) the rate of relapse is particularly high in patients with PJI caused by multidrug-resistant pathogen [9–11]; (iii) bacteriophages and antibiotics are synergistic [12,13]; (iv) there is no cross-resistance between antibiotic resistance and bacteriophage resistance [6–12]; (v) some in vitro and animal models demonstrated that bacteriophages could have an anti-biofilm activity [6,13,14]; and (vi) recent human and animal trials using phage therapy have not shown any local tissue toxicity or any adverse effects to the host [15–20].

Bacteriophages were used in the 1970s in France [21] and remained a popular treatment throughout the 20th century in Eastern Europe (Poland) and the former Soviet Union (Georgia, Russia) in patients with relapsing osteomyelitis. Few case series have been published in the literature, including patients with pyogenic native joint infection, chronic osteomyelitis, suppuration after bone fracture and diabetic foot osteomyelitis [22–26].

In preclinical studies using animal models for PJI bacteriophages were found to prevent bacterial adhesion and also effectively disrupt the formation of biofilm [13,27]. Animal studies also have proven synergism between antibiotics and bacteriophages [13]. In another animal study, Kishor et al. [26] studied the efficacy of several phages used in conjunction as a treatment modality for chronic osteomyelitis caused by MRSA in rabbits. The study showed that the combination of specific phages selected based on their virulence against various clinical MRSA strains was effective in eradicating the infection, thus suggesting that a "tailor-made cocktail" of phages can alone be effective in targeting specific bacteria in the setting of a chronic infection. Some of the issues with current PJI animal models are that they don't replicate mechanical stresses occurring in clinical settings and, therefore, may not be fully representative of clinical situations.

Wright et al. conducted a randomized, double-blind clinical trial using bacteriophages in humans [28]. They studied the effect of the combination cocktail of six phages targeting *P. aeruginosa* in the treatment of antibiotic-resistant chronic otitis media infection. The authors achieved measurable therapeutic effects with minimal dosing, thus suggesting a promising role for phage therapy in treating antibiotic-resistant infections.

No case series including patients with PJI has been published (we retrieved only two cases from a French series of bone and joint infection treated with bacteriophages) [6]. In the Georgian practice, specific phages mixtures are used, such as the "pyophage" cocktail that contains phages against *S. aureus*, *Streptococcus*, *Proteus*, *P. aeruginosa* and *Escherichia coli* (*E. coli*) or specific bacteriophages targeting specifically staphylococci, as the Sb-1 phage (that could be imported in the USA), the bacteriophage K or the bacteriophage ISP [22]. In Poland, phage(s) are selected from a bank based on their activity on the patient's strain to adapt the treatment (personal medicine) and to ensure antibacterial activity of phages used [23,24]. All these bacteriophages are classically prepared with a bacterial inoculum, in vitro infection with the bacteriophage and purification of the preparation in aliquots at 10^7 to 10^8 PFU/mL. These preparations are approved by local authorities but do not respect European "good manufacturing practice" (GMP) standards for conducting clinical trials and targeting Market Authorizations (MA). Indeed, the final product requires total elimination of bacterial components that are

generated during the production process, such as toxins, in order to limit pyrogenicity and adverse events that may arise during phage administration/use, especially when the phage is administered intravenously or directly in a joint cavity. As a consequence, bacteriophages are currently not injected directly into the joint in patients with PJI but locally throughout the fistula and/or orally in patients with chronic osteomyelitis [23–25].

Recently, an European multicentric clinical trial evaluating phage therapy of burn wound infections has been done using *P. aeruginosa* and *E. coli* bacteriophages from a GMP French bioproduction process that was implemented according to European Medicine Agency standards (ClinicalTrials.gov Identifier: NCT02116010). The French team from the Lyon bone joint infection (BJI) study group (also called CRIOAc Lyon, a regional reference center for the treatment of complex bone and joint infection in France; http://www.crioac-lyon.fr) has treated as salvage therapy, under the supervision of the French health authorities, three patients with chronic bone and joint infection (one osteomyelitis due to extensively drug-resistant *P. aeruginosa*; and two *S. aureus* PJI) with bacteriophages that follows the same process of production. For all the patients, the cocktail was personalized and selected based on the bacteriophage susceptibility of the clinical isolates (phagogram; similar principle as antibiogram but with bacteriophages) that was isolated after a joint puncture before the surgery. The two patients with PJI had chronic infection with purulent discharge and were treated with debridement antibiotics and implant retention (DAIR) supplemented with a direct administration of the bacteriophage *S. aureus* cocktail in the joint cavity at the end of the procedure. Both patients are doing well during the follow-up of 12 months and 3 months, respectively (unpublished data). A randomized clinical trial called PHAGOS will start soon in France, to evaluate the addition of *S. aureus* bacteriophage in patients with relapsing *S. aureus* PJI. The availability of *P. aeruginosa*, *E. coli* and *S. aureus* with GMP standard in France is a great opportunity to evaluate the phage therapy as an additive treatment in patients with PJI, especially in patients with multidrug-resistant PJI.

Although phage treatment looks promising and safe, further research is needed to understand immunogenicity and answer the remaining questions related to treatment by phage such as timing, duration, methods of delivery and route of administration. Limitations of present studies include the reduced spectrum of bacteria tested, which are limited to MRSA and *P. aeruginosa*, without considering coagulase-negative staphylococci (CoNS), which substantially contribute to PJI onset [29]. In addition to these there is a concern with regards to the immunogenicity of phages and resulting diminished therapeutic efficacy [30].

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PART X

PEDIATRICS

Section 1: Prevention

Section 2: Diagnostic

Section 3: Treatment

Prevention

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QUESTION 1: Are pediatric patients on oral or intravenous steroids at an increased risk of developing septic arthritis?

RECOMMENDATION: Unknown. There is no definitive link between the use of oral or intravenous steroids and development of septic arthritis in pediatric patients.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 5%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

Septic arthritis is an infection of joints that spreads through systemic or local bacterial, viral or fungal infection. The overall prevalence of septic arthritis is relatively higher among children who are less than 4 years old. The incidence of septic arthritis has been reported to be 10 cases per 100,000 population and as high as 20 to 70 cases per 100,000 in patients with rheumatoid arthritis in the USA. The disease usually spreads through hematogenous system mainly due to intravenous drug use or prolonged use of a catheter and low immunity. The most common predisposing conditions that can develop into septic arthritis are rheumatoid arthritis, gout or osteoarthritis. In children, the hip is most commonly affected joint by septic arthritis as compared to the knee in adults accounting for 50% cases.

Computerized research of databases (PubMed, Medline Ovid and Google Scholar) was used for the literature review from 1950 to 2018. The shortage of literature could not directly link IV or oral steroid therapy as a risk factor for children to develop septic arthritis as an adverse reaction. Many randomized clinical trials were, however, found to be in favor of the prolonged use of IV and oral corticosteroid to avoid complications in pediatric patients suffering from septic arthritis and no further complications were observed that lead to the worsening of this disease [1–3]. There is still a debate whether immunosuppressive drugs, such as corticosteroids and cytotoxic agents, increase the risk for septic arthritis [4]. The potential association between administration of steroids and septic arthritis may be explained by the fact that steroids reduce the body's immunity and ability to fight infection [4]. One of the indirect causes of septic arthritis was found to be iatrogenic in 41.8% of adults, and the number of iatrogenic infections in Iceland increased from 2.8 cases/year in 1990–1994 to 9.0 cases/year in 1998–2002 ($p<0.01$) [5]. These iatrogenic infections can be linked to the use of unsterile intra-articular injections, possible use of contaminated needles or a break in the sterility during arthroscopic procedures [6,7].

The study conducted in the USA reported 32 cases of septic arthritis due to fungus-contaminated methylprednisolone vials [8]. However, these studies lacked proper evidence as these were descriptive in nature. These studies also did not fulfill our inclusion and exclusion criteria as it does not show a direct relationship of septic arthritis with steroid therapy rather than being an iatrogenic infection.

A case report published in 1957 reported septic arthritis as a reaction to steroid therapy in a woman who was 34 years old; she had been receiving corticotrophin, cortisone, hydrocortisone and prednisolone at various times in a year for the treatment of lupus erythematosus. A similar presentation was found in a man 54 years old suffering from exfoliative dermatitis and was getting treated with the same medicine. The steroid therapy resulted in septic arthritis of one knee and both hands including disfigurement of his fingers. Unfortunately, this study could not hold much evidence as it had a weak study design and the lowest number of reported cases. It also included adult patients so it cannot be generalized to children [9].

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Diagnostic

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QUESTION 1: What are the essential tests that need to be done in pediatric patients with joint infections?

RECOMMENDATION: Essential laboratory tests include serum C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), white blood cell (WBC) count, blood cultures, synovial fluid analysis and culture of tissue and/or synovial fluid. Further molecular testing and leucocyte esterase (LE) testing may have a role and warrant further research. Imaging studies include ultrasound in the hip joint. Symptoms lasting over a week warrant investigation with plain radiography. Magnetic resonance imaging (MRI) and bone scanning may have value in confirmation of the diagnosis in some patients.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 88%, Disagree: 6%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Diagnostic evaluation of children with suspected joint infection or osteomyelitis should include CRP, WBC count and ESR [1]. CRP is valuable as a negative predictive tool since CRP < 1.0 mg/dL helps rule out the diagnosis of septic arthritis (SA) with an accuracy of 87% [2].

Synovial fluid aspiration should be performed. Samples should be transported in a heparinized syringe or pediatric culture bottles to prevent the clotting and enumeration of leukocytes [3]. Cell count and differential, gram stain and culture of the obtained synovial fluid are important steps in diagnostic work up of pediatric patients with SA [4,5].

A wide range of organisms can cause SA in pediatric patients. Thus, culture samples should be sent for both aerobic and anaerobic cultures. If an infection with unusual organisms is suspected, then a specialized culture medium may need to be used. For example, SA caused by *Kingella kingae* may require the use of cell lysis culture bottles for isolation of the organism [3]. If there is clinical suspicion for infection by *Neissena gonorrhoeae;* rectal, oropharyngeal, urogenital cultures and urine deoxyribonucleic acid (DNA) analysis are indicated [6,7].

In infants and young children, subperiosteal needle aspiration can be performed if point tenderness exists [3]. Although a WBC count > 50,000-60,000/mm^3 is typically expected, a synovial fluid leukocyte density of 5,000-8,000 cells/mm^3 has been found in cases of pediatric SA [8].

Conventional radiographs of the affected joint should also be taken in pediatric patients as imaging may show signs of osteomyelitis [9–11]. Plain radiographs are typically normal [12]. Ultrasound evaluation of the affected joint has been reported to be useful in the diagnostic work-up of SA, especially of the hip [12]. In one study, normal hip ultrasound was found to have a negative predictive value of 100% for SA [13]. In some circumstances additional imaging may be needed. MRI is the cross-sectional imaging modality of choice in pediatric patients with more than 90% sensitivity for diagnosis of SA. Sub-periosteal or soft tissue collections of pus that may require surgical drainage can be better and earlier detected on the MRI images. In the setting of acute osteomyelitis, decreased signal on T1-weighted images and increased signal on T2-weighted images is a pertinent finding [3]. MRI with and without gadolinium contrast should be ordered to identify the presence of osteoarticular infection and assess the perfusion status of the joint [14].

Radionucleotide scanning is widely used to diagnose osteomyelitis early when plain radiographs appear normal. Technetium-99m (99mTc) scintigraphy is the most common used type of radionucleotide imaging. Browne et al. reported that bone scans fail to detect about half of the cases of methicillin-resistant *Staphylococcus aureus* (MRSA) osteomyelitis [9]. Indium 111–labeled leukocyte scans are another option for diagnosis of osteomyelitis [15]. At present, there is no evidence that supports superiority of radionucleotide scanning over MRI.

Molecular analyses of the synovial fluid using polymerase chain reaction (PCR) or next generation sequencing (NGS) may provide a useful adjunct to conventional culture for the identification of the infective organisms. These assays may be effective in the detection of atypical bacteria, such as mycobacterium, anaerobic pathogens and facilitate pathogen identification in culture-negative disease [7].

The use of serum or synovial molecular markers in the diagnosis of SA has been explored. Procalcitonin is an emerging biomarker for the diagnosis of SA with a high specificity for detecting joint infections, but studies have only been conducted in adults [16–19]. Another biomarker that has been explored in the setting of pediatric SA is LE. LE has been in clinical use for over 30 years, mostly as a point-of-care test for the diagnosis of urinary tract infection. The first application of this test in orthopaedic patient population was explored by Parvizi et al. [20]. In the latter study, investigators reported over 80% sensitivity and 100% specificity with the use of LE dipstick testing for diagnosis of periprosthetic joint infection (PJI). A recent study demonstrated that LE is a valuable test for diagnosis of native SA, but evidence for its efficacy in the pediatric age group is sparse [21].

Finally, the role of interleukin-6 (IL-6), a cytokine that is released by fibroblasts, has also been explored in the pediatric patient population. IL-6 is an acute-phase reactant that is thought to play a role in increasing CRP production by the liver [22]. IL-6 may be detected earlier than CRP in bone and joint infections, however, its associated cost and limited availability in the clinical setting have prevented it from becoming a mainstay in diagnosis of orthopaedic infections [22,23].

In conclusion, it appears that conventional serum tests, namely CRP and ESR, plain radiographs and synovial fluid analysis are the most important tests in work-up of a pediatric patient with suspected SA and/or osteomyelitis. Molecular biomarkers or techniques involving DNA sequencing may play a role in facilitating

diagnosis, as they have demonstrated superior sensitivity over conventional cultures.

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QUESTION 2: Are there conditions where the erythrocyte sedimentation rate (ESR) and other blood tests are unreliable for diagnosis of pediatric musculoskeletal infections?

RECOMMENDATION: Yes. Serum tests including ESR, C-reactive protein (CRP) and absolute white blood cell (WBC) count might be unreliable for diagnosis of pediatric musculoskeletal infections in neonates, patients with rheumatological disease, post-trauma, post-surgery, patients with Lyme arthritis and those receiving intravenous immunoglobulin (IVIG) administration.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 88%, Disagree: 3%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

Various serology tests including WBC count, ESR and CRP are traditionally used to diagnose septic arthritis (SA)/osteomyelitis (OM) in children. Their diagnostic value is less than synovial fluid analysis and cultures that usually are utilized to prove the infection. ESR and CRP are almost always elevated in any inflammatory process (trauma, rheumatologic disease) with low specificity for infection [1,2].

Leukocytosis is not a typical feature in children with SA [3]. It has been shown that studies including more SA rather than OM have a lower rate of leukocytosis [4]. Results of an evidence-based study showed that overall diagnostic accuracy of peripheral WBC count for SA is not acceptable regardless of selected cutoff point [1].

The challenging age group in children is neonates and young infants in whom the infection is caused by organisms, such as coagulase-negative Staphylococci [4]. Owing to the non-characteristic features of osteoarticular infection, Sankaran et al. in a prospective study reported that fever, poor feeding and irritability are seen in less than 30% of infants with SA. Beside the paucity of sign and symptoms in this study, neutrophil count was found to be normal in 70% [5].

CRP is more sensitive than ESR for diagnosis of infection; its level rising as soon as six hours after disease initiation. Different studies have shown its usefulness in the diagnosis of SA [6,7], resolution of infection in neonates [8] and its ability to differentiate transient synovitis of the hip from SA [9]. Levine et al. reported that ESR and CRP are better as negative predictors for SA, particularly when the CRP level is less than 1mg/dL with an accuracy of less than 85% [8].

Lyme arthritis in children may be associated with clinical findings similar to SA. CRP and ESR levels are reported to be increased in 64% to 100% of patients with Lyme arthritis, respectively [10,11]. CRP and ESR were not found to be useful tests to differentiate Lyme disease and SA [12]. Administration of IVIG in children can also result in increased levels of ESR, interfering with diagnosis of SA/OM and rendering the test ineffective in monitoring response to treatment [13].

Even though CRP and WBC counts of synovial samples are believed to be useful tests for diagnosis of SA and distinguishing it from juvenile inflammatory arthritis (JIA), a recent report demonstrates that these tests might not be sufficiently specific as there is significant overlap in the value of these tests in both conditions [14].

In addition, the levels of CRP and ESR may be elevated following trauma and after surgical procedures [15], rendering these tests less useful in post-trauma and postoperative periods.

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QUESTION 3: For pediatric patients with suspected septic arthritis (SA), does the clinical criteria override inconclusive laboratory tests?

RECOMMENDATION: For pediatric patients with suspected SA, the clinical criteria override inconclusive laboratory tests.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 91%, Disagree: 2%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

It is well known that there are no standard tests that can accurately diagnose SA in children [1–7]. Thus, it is not uncommon to face a situation where the diagnosis of SA is strongly suspected, but laboratory tests remain inconclusive [3,4]. Among all the existing diagnostic tests for septic arthritis, isolation of infective organisms from the synovial joint is considered as the gold standard for this condition [3,5,6]. However, the latter can hardly be considered a gold standard as the probability of isolating an infective microorganism from the synovial fluid of patients with SA ranges from 22%-82% [7]. Culture results are affected by numerous factors including antibiotic administration and the virulence of the infective organism.

To improve the yield of a culture, it is recommended that antibiotic treatment is initiated after joint aspiration has been performed. In case of negative culture, laboratory tests, clinical symptoms and radiological signs are important for the diagnosis of SA [1,7]. As no single diagnostic test for SA in children exists [8], it is recommended that the diagnosis of SA should rest on the opinion of experienced clinicians and override the laboratory tests [1,3,4]. A systematic review revealed that, despite the use of laboratory investigations, the gold standard for the diagnosis of SA is the level of clinical suspicion of a physician experienced in the management of pediatric patients with musculoskeletal infections [3,4,8].

Although analysis of the synovial fluid can be useful in the diagnosis of SA in children, aspiration of the joint may require administration of general anesthesia and is complicated. The decision to perform aspiration should rest with the clinician and be determined based on the degree of suspicion for SA. Diagnosis of SA should rely on less invasive tests as much as possible [5].

Despite the extensive literature investigating the clinical and laboratory features of septic arthritis, the number of studies that exist on the significance of clinical features and laboratory tests for diagnosis of SA in children is limited.

Among the eight published studies, one is a systematic review, two are retrospective studies, two are review articles, one is a community-based epidemiological study and two are case series [1–8]. Based on the evaluation of the available literature, we are unable to determine the most effective diagnostic protocol for SA in children. Among the reviewed studies, one proposes that not all children can be classified as having or not having SA on the basis of historical, clinical, laboratory or radiologic findings [8]. The latter raises the need for additional tests, such as joint aspiration.

Another study endorses the same principle recommending that any patient without clear-cut evidence for SA, or lack thereof, needs an examination of the joint fluid for diagnosis [1]. Another study reported that the diagnosis is rarely established by the history and physical examination, and the clinician is led to rely on ancillary tests, specifically the white blood cell (WBC) count from peripheral blood and other serological markers for inflammation, such as the erythrocyte sedimentation rate [4]. A retrospective study examined the incidence, etiology and clinical features of septic arthritis in children less than 24 months and concluded that the diagnosis of SA in children needed to be made based on a high index of suspicion and could not be excluded based on lack of fever and normal laboratory tests [2].

Based on our understanding of the literature, and in the absence of an absolute test, it appears that the diagnosis of SA in children needs to be made using a combination of clinical findings, laboratory tests and appropriate imaging. For patients with equivocal findings, clinical suspicion should override laboratory findings, because missing SA in a child, especially when caused by a virulent organism, can have serious consequences.

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QUESTION 4: Is there a role for arthrocentesis (joint puncture) of an infected joint in a pediatric patient?

RECOMMENDATION: Yes. Arthrocentesis of an infected joint is effective for decompression of the joint. However, some children need arthrotomy.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 83%, Disagree: 11%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Arthrocentesis (joint puncture) is one of the most valuable procedures for the diagnosis and treatment of joint diseases [1]. In children with septic arthritis (SA), arthrocentesis can be very useful for both diagnosis and as means of treatment [2,3]. It is safe and simple, but approaching the joint correctly, especially of the hip, is not possible for all physicians in emergency departments [4].

In a child with acutely swollen, red, painful joint and fever, if C-reactive protein (CRP) > 20mg/dL or erythrocyte sedimentation rate (ESR) > 20mm/h, then arthrocentesis may be indicated to confirm the diagnosis [5]. Arthrocentesis is also used as the treatment of SA in combination with antibiotic therapy. Ultrasound-guided aspiration of the hip evacuates pus, reduces damage to the articular surfaces, differentiates joint sepsis from other arthritides and helps direct antibiotic treatment [6,7]. Furthermore, there is a concern about the adverse effect of emergent open arthrotomy in severely inflamed joints, and it is debatable whether early decompressive arthrotomy is always useful [8–11].

In a retrospective study, hip arthrocentesis was found to avert the need for invasive surgery in more than 80 % of children (ranging from 3 months to 15 years of age) in a cohort of 261 culture-positive patients with SA. Outcome was comparable between arthrotomy and non-arthrotomy group. The study found that in the case of adjacent osteomyelitis, arthrotomy was more useful [12]. The results are supported by another study by Journeau et al. that reported favorable outcome in about 90% of the patients with hip arthrocentesis. They identified CRP > 100 mg/L, polymorphonuclear cell > 15,000, and ESR > 25 mm/hr as predictive of the need for arthrotomy [13].

In a prospective randomized trial, 201 consecutive children with the diagnosis of SA, arthrocentesis and arthrotomy were compared, and the patients were followed for one year. There were no differences regarding clinical outcome in any of the groups; hospital stay was lower in arthrocentesis group [8]. Smith et al. in a randomized control trial reported similar results for outcome of arthrotomy vs. arthrocentesis in 61 children with SA of the shoulder [10]. The findings of the latter study are also reflected in another study by Pääkkönen et al. involving nine children with SA affecting the shoulder [14].

Existing evidence for knee joint is different. Arthroscopic irrigation and decompression has been found to be successful in the majority of patients. The procedure can be performed through a single portal and without the need for a repeat procedure. In a retrospective study, around 40% of children older than three years who underwent a knee arthrocentesis required further arthrotomy to eradicate the infection and high initial CRP levels were identified as a predictor of aspiration failure [15].

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QUESTION 5: Is there a role for percutaneous bone sampling (biopsy) for microbiological diagnosis of septic arthritis/osteomyelitis (OM)? If so, when should this be performed?

RECOMMENDATION: Yes. Percutaneous bone sampling (biopsy) is very safe and cost-effective and can be obtained from any site under the guidance of fluoroscopy or computed tomography (CT). It has a low sensitivity for microbiological diagnosis of OM that can be enhanced by the addition of histopathological examination. Literature suggests that bone sampling should be performed before initiating empirical antibiotic therapy.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 88%, Disagree: 7%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

OM is described as inflammation of the bone marrow and adjoining bone and is usually related with cortical and trabecular destruction. It can be caused by bacteria, fungi and a variety of other organisms [1]. Prompt identification and treatment of OM is necessary since undiagnosed cases can result in chronic pain, amputation and death. Even though clinical symptoms, inflammatory serological markers and imaging, such as magnetic resonance imaging (MRI), play an essential role in reaching a diagnosis of OM, the most important aspect of diagnosis relies on isolation of the infective organism from the infection site [2–4]. Pathogen identification and determination of its antibiotic susceptibility are paramount for successful treatment with antimicrobial therapy. Blood cultures may also be positive in a small number of patients with OM, which can guide antimicrobial therapy, so definite diagnosis and suitable therapy depend on tissue samples collected through bone biopsy [4].

Although surgical biopsy is also an option for confirming the diagnosis, percutaneous biopsy with fluoroscopic or computed tomography (CT) guidance has been proven to be a more reasonable, faster and more cost-effective modality with fewer complications [5,6]. The first percutaneous vertebral bone biopsy was performed by Ball in 1934. The use of image guidance was first seen with radiography in 1949, fluoroscopy in 1969, CT in 1981, MRI in 1986 and CT fluoroscopy in 1996 [6].

Literature review from the 1990's and early 2000's stated the accuracy of a percutaneous biopsy of vertebral lesions guided with CT or fluoroscopy ranged from 88% to 100% [6]. The recent and most comprehensive retrospective review done by Sehn and Gilula reported that 63 of 113 cases were positive when samples were tested histologically (55.7%) and only 28 of the 92 cases were positive when samples were investigated microbiologically (30.4%). Culture and/or pathology review was positive in 73 (64.6%) of the 113 cases. Pathology review along with culture of biopsy specimen supported a diagnosis of OM in 64.6% of investigated cases. However, the age of the participants ranged from 1 to 92 years [7]. This is in contrast to the study done in the 1990s and early 2000s [6].

Ballah et al. reported that there were 26 biopsies performed, 21 out of 26 biopsies were diagnostic (81%); 2/26 (8%) were false-negative extracting nonlesional tissue, 2/26 (8%) were nondiagnostic and 1/26 (4%) were technically unsuccessful. The diagnoses were as follows: 12/26 biopsies (46%) were OM; 3/26 (11%) biopsies were Langerhans cell histiocytosis; 3/26 biopsies (11%) were normal bone; 2/26 (8%) biopsies were malignant tumors and 1/26 (4%) biopsies were osteoblastoma. Of 12 children with OM only 3 had a positive culture; 9/12 (75%) children had a negative culture. They did not report any p-value or confidence interval. They concluded that percutaneous CT guided vertebral bone biopsy is safe in children with a high degree of diagnostic accuracy [8].

A systematic review and meta-analysis of 7 studies (later excluded 2 studies) indicated that image-guided percutaneous needle aspiration biopsy has a high specificity (99.9%) and, therefore, is quite effective when positive. However, it has low sensitivity (52.2%) and can miss a substantial proportion of patients. Image-guided spinal biopsy had a diagnostic odds ratio (DOR) of 45.50 (95% confidence interval [CI], 13.66–151.56), a likelihood ratio of positive test (LRP) of 16.76 (95% CI, 5.51–50.95), a likelihood ratio of negative test (LRN) of 0.39 (95% CI, 0.24–0.64), a sensitivity of 52.2% (95% CI, 45.8–58.5) and a specificity of 99.9% (95% CI, 94.5–100). The results of this study strengthen

the importance of image-guided percutaneous spinal biopsy [9].

Wu et al. observed that out of 41 (age range 3 to 82 years) histologically positive cases of OM, 14 (34%) cases were positive at culture. The proportion of positive culture results in confirmed cases of OM on the basis of histology was low. Patients who were on antimicrobial therapy in a 24 hour period of the biopsy, 24% had a positive culture, and the patients who were not on antibiotics had a 42% culture positivity rate. Larger prospective studies are required to investigate this finding further. They also advised or requested physicians to hold antibiotics for at least 24 hours before the biopsy [10].

Rankine et al. performed a retrospective study on 20 patients who had percutaneous spinal biopsies, with 8 out of 20 patients (40%) on antibiotics before the biopsy. An organism was isolated in 8 out of 20 cases (40%). Out of 8 patients on antibiotics, an organism was isolated in only 2 cases (25%). The result of the biopsy helped to modify the treatment in 7 of the 20 patients (35%). They also suggested that spinal biopsy should be done before starting antibiotic and a sample should be sent for both microbiology and histopathology [11].

Ng et al. reviewed the histopathological, cytological and microbiological results of patients who underwent bone and para-osseous biopsies between July 1977 and March 1996. The 502 biopsies were taken from 477 patients (age range for male patients was 5-86 years and for female patients was 2-86 years). Tumors were reported in 40% of the biopsies and infection in 16%. The latter study confirms the importance of bone biopsy in confirming diagnosis of infection and also detecting the presence of neoplasm, a differential diagnosis that needs to be born in mind when encountering pediatric patients suspected of infection. A bone biopsy can be taken from any site under the guidance of fluoroscopy or CT [12].

In conclusion, our extensive search of the literature has revealed one study evaluating the role of bone biopsy in children with the remainder of the studies being performed in an adult population. Based on the available evidence, we recommend that percutaneous bone biopsy under fluoroscopic or CT guidance is a reasonable, fast and cost-effective modality for diagnosis of OM and differentiating infection from neoplasm. It carries low complication rate but the ability of this test to isolate the infective organism in OM remains low. The above studies suggest that percutaneous bone biopsy shows high specificity but low sensitivity in microbiological diagnosis of OM but the combining results of microbiological examination with histological evaluation of the samples enhances the sensitivity. Literature also suggests that bone biopsy should be performed before initiating empirical antibiotic therapy in order to increase its yield for isolation of the infective organism.

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QUESTION 6: Is there any role for polymerase chain reaction (PCR) or molecular testing in pediatric musculoskeletal infection (PMSI)?

RECOMMENDATION: PCR may be a useful diagnostic adjunct with the potential to expedite a preliminary diagnosis of PMSI in comparison to the use of microbiological culture alone. Furthermore, PCR can enable pathogen identification in cases where the organism is indolent, fastidious or difficult to culture. However, data remains sparse and further research is needed to standardize molecular techniques, minimize contamination and explore emerging molecular methods that are primer-independent.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The diagnosis of musculoskeletal infection is typically based on pertinent clinical findings, synovial fluid analysis and a positive gram stain or culture confirming the microbial identity of a pathogen [1]. Although culture results are used to identify the infecting organism and determine antimicrobial sensitivity, culture is often limited by sampling methodology, processing issues, early antibiotic administration, and/or the presence of hard to culture organisms [2–4]. PCR and other molecular techniques have been investigated to a limited

degree as diagnostic tools and are showing promise for improving PMSI diagnosis.

Evidence for the diagnostic use of PCR in PMSI is sparse. In a prospective study exploring the utility of PCR, Verdier et al. enrolled 171 pediatric patients with osteoarticular infection (OAI). From this cohort, 64 culture-positive specimens were identified, of which 9 cases were positive for *Kingella kingae*. When the 107 culture-negative specimens were tested with PCR, 15 additional cases of *Kingella kingae* were detected [5]. Similarly, Chometon et al. conducted a study of 131 patients with acute pediatric OAI in a single hospital and found that pathogen identification improved from 45% by culture alone to 66% with both culture and PCR testing [6].

Ferroni et al. performed a prospective study with 197 acute pediatric OAI cases in a single hospital and found that the use of PCR in addition to culture and histology increased bacterial diagnosis by 54%.

There is additional evidence for the utility of PCR aiding diagnosis of musculoskeletal infection from studies examining adult cases. However, the reported sensitivity of PCR varies widely in the literature from 43.8% to 92.5% and specificity ranges from 92.9% to 100% [7–9]. Despite this variation, investigators consistently conclude that the rapid availability of the results (<1 day) make PCR an adjunctive tool for guiding early treatment prior to the availability of culture results [7,8], especially in the setting of a negative culture [9]. It should be noted that these studies used different standards to compare to PCR performance; Bonilla et al. and Fenollar et al. used culture results as their gold standard, while Fihman et al. used clinician diagnostic judgment based on predetermined factors [7,9]. This significant inconsistency renders the results difficult to compare and interpret across studies.

PCR has also shown promise as a valuable tool for diagnosing tuberculosis affecting the bones and joints [10–12]. *Mycobacterium tuberculosis* is a particularly difficult organism to culture because false-negative results are relatively common. Therefore, a rapid, reliable diagnostic test is still needed. A study of 24 samples (21 patients) showed that PCR had 100% sensitivity and 87.5% specificity for identifying tuberculous disease affecting the bones and joints. However, two false-positive results were seen in patients who had previously been diagnosed with tuberculosis [10].

An infected joint can rapidly progress into a medical emergency. Rapid molecular diagnostic tools could play a crucial role in identifying and treating the infection promptly [13]. PCR is a sensitive, rapid and widely-available molecular methodology that can detect microbial pathogens in clinical samples. However, in order to obtain reliable and consistent results it is necessary to standardize PCR preparation protocols and take care to avoid contamination [1,13].

Further research is needed to investigate the role that PCR and other molecular methods can play in identifying a pathogen.

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QUESTION 7: How can we differentiate between sickle cell crisis and septic arthritis/osteomyelitis (OM)?

RECOMMENDATION: A combination of clinical, laboratory and imaging studies are all needed for differentiating between sickle cell crisis and infection. A positive aspiration for infection from the joint or periosteum confirms the presence of infection while sequential ultrasounds in the absence of sub-periosteal fluid collection favor sickle cell crisis. Tri-phasic bone scan in the first 24 hours can differentiate vaso-occlusive crisis (VOC) from acute infection. Contrast-enhanced magnetic resonance imaging (MRI) is fairly accurate in differentiating infection from infarction.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 87%, Disagree: 0%, Abstain: 13% (Super Majority, Strong Consensus)

RATIONALE

Differentiating bone and joint infection from osteonecrosis (ON) in sickle cell disease (SCD) can be very challenging. Clinical presentation is an important tool in distinguishing OM from VOC in SCD: sudden, often severe pain; no or low-grade fever of less than 100 F (<38 c); inflam-

matory markers only mildly elevated; and elevated HB/HCT ratio are all indicative of crisis and ON [1–3]. Also, pain in more than one site is more likely to be a crisis and not OM [4,5].

Inusa et al. [6] in a retrospective study demonstrated that mean initial white blood cell count was 14.9 in VOC and 17.8 in OM. They reported mean C-reactive protein (CRP) as the more informative test in differentiating OM from VOC–86.4 vs. 39.8. Therefore, CRP should be included in the risk criteria for infection in an SCD patient with fever [7,8]. Radiographs in early phases of OM or VOC are usually normal, with periosteal reaction showing up in both conditions within the first 2 weeks [4,9].

Ultrasound scans alone can diagnose OM in SCD cases with 74% sensitivity and 63% specificity [10]. Ultrasound scan within the first six days shows periosteal elevation and/or fluid collection in 76% of OM, while 91% of VOC cases show no evidence of fluid collection. Repeat ultrasound is needed to confirm the diagnosis of VOC when fluid collection remains negative [6].

Combination of ultrasound and CRP was found to be a reliable, cost-effective measure in distinguishing OM from VOC [6]. Triphasic isotope bone scans and labeled WBC scans can be helpful in later stages [11–14]. Sequential radionuclide bone marrow scanning and bone scan within the first 24 hours differentiate bone infarction from acute infection [15,16].

T1-weighted MRI has low intensity in the medullary infarct and high intensity in T2-weighted images [4,11]. Contrast material enhancement on MRI may distinguish accurately between infection and infarction [17]. Un-enhanced bone marrow signal intensity on fat-saturated MRI images is not a reliable criterion for differentiation of infection from infarction according to Delgado [18].

Aspiration of pus from the subperiosteal region or joint, or positive blood culture remains the gold standard for diagnosing infection in SCD, bearing in mind that a negative blood culture does not rule out infection [8,19,20].

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Treatment

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QUESTION 1: What are the indications for surgical intervention in cases of osteomyelitis/septic arthritis? How should treatment progress and resolution be monitored?

RECOMMENDATION: Septic arthritis is an orthopaedic emergency and needs prompt surgical treatment. Based on current evidence, there are no clear indications for the timing of surgical intervention in cases of osteomyelitis. The current literature does suggest monitoring disease progression, treatment efficacy and resolution by trending C-reactive protein (CRP) levels.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 91%, Disagree: 3%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

The treatment of musculoskeletal infections in children has long been debated. Evidence has shown that it can be appropriate to treat this condition medically. However, surgery can play a critical therapeutic role for patients not responding to medical treatment or those presenting with massive bioburden in the joint that may require evacuation.

Osteomyelitis in the pediatric population often has overlapping clinical features with other diseases, making its diagnosis challenging [1]. Not only are the clinical presentations diverse, the epidemiologic aspects of the pathology also play a critical role in its therapy. Patient age, sex, socioeconomic status and even geographical location all point to different etiologies, making treatment choices challenging [1,2]. Patients living in the United States can be at particular risk of aggressive osteomyelitis infections due to the presence of highly virulent strains of methicillin-resistant *Staphylococcus aureus* (MRSA). Ninety percent of MRSA isolates found in the U.S. are related to the USA300 strain which is positive for *pvl* and *fnbB* genes–coding for the Panton-Valentine Leucocidin toxin and fibronectin binding factor respectively [3]. Patients contracting strains such as these are at increased risk of subperiosteal abscess formation, septic thrombophlebitis, endocarditis and large muscle abscesses [3]. Another pathogen, *Kingella kingae*, has also recently emerged as an etiology of osteomyelitis and septic arthritis with a milder clinical presentation as well as lower inflammatory markers and white-blood cell (WBC) counts [4]. This further emphasizes the diversity in which these conditions can present.

Because of the multifaceted nature of osteomyelitis, care of these patients requires a coordinated, multidisciplinary approach in order to avoid potentially devastating complications of a missed osteomyelitis diagnosis [1]. As with many conditions in medicine, early diagnosis and treatment initiation are paramount. Unfortunately, there are no gold standard tests to aid in the diagnosis of septic arthritis or osteomyelitis in the pediatric patient population [5]. Additionally, the lack of clear-cut surgical indications makes treatment plans complicated [1,6–9].

Osteomyelitis was found to be concomitant with septic arthritis in about 30% of cases [1,3]. Typically, bacteria seed in the metaphyseal region of long bones where capillaries make sharp turns resulting in serpentine routes of blood flow [1,3,5]. If the infection develops in the intracapsular portion of metaphyseal bone (i.e., proximal femur, humerus, radius or lateral distal tibia) there is a higher likelihood of extension into the joint space [1,3]. Joint space involvement creates an increase in intra-articular pressure, recruitment of leukocytes and subsequent release of cytokines, which can cause cartilage damage in as little as eight hours [4,10].

Proponents for surgical intervention have argued that the operative intervention can halt the disease progression [1,6,11]. Surgery and debridement of the joint can reduce the likelihood for osteonecrosis by enhancing the vascular supply to the bone, thereby allowing for improved antibiotic delivery and penetration to the site of infection [6]. Likewise, with osteoarticular involvement, decompressing and washing out the joint helps stem permanent damage by decreasing intra-articular pressure and reducing proteolytic enzymes resulting in degradation of the cartilage and sub-chondral bone [10,11].

Despite these valid arguments, studies have not been conducted that effectively define surgical indications for osteomyelitis and septic arthritis. Indications for surgery in the literature are based on expert opinions, case series and cohort studies with none providing evidence-based clinical guidelines for surgical intervention in the case of osteomyelitis [6,7,9]. Additionally, the surgical procedures used for osteomyelitis are diverse, ranging from bone biopsy and subperiosteal abscess drainage to more involved procedures, such as the creation of a cortical window and extensive debridement [1]. Dartnell et al. conducted a systematic review of the literature and found very little evidence to support surgical intervention in pediatric patients with osteomyelitis and/or septic arthritis due to a lack of randomized controlled trials [8]. At best, current recommendations for surgery include [1,6–8,12]:

- Failure to improve in 48-72 hours despite antibiotic treatment
- Presence of frank pus on aspiration of the joint
- Identification of sequestered abscess

However, none of these recommendations come with quantitative evidence from randomized controlled studies.

Septic arthritis is considered an orthopaedic emergency and necessitates prompt treatment [13–15]. Across the current literature, it is well agreed that septic arthritis requires surgical removal of the inciting materials [5,10]. Guidelines and appropriate randomized trials to establish statistical evidence are still lacking. Moreover, numerous suggestions of the exact joint decompression technique exist (i.e., arthrotomy versus arthroscopy versus needle aspiration).

El-Sayed et al. conducted a prospective controlled study to compare hip arthrotomy versus arthroscopy in the setting of septic

hip arthritis [13]. Open arthrotomy had been considered the gold standard at the time of his study. The latter study reported no statistical differences in clinical results (according to Bennett's clinical assessment criteria), such as prolonged post-operative joint aches, joint range of motion limitations or infection recurrence [13]. Mean hospital length of stay was shorter for the arthroscopic group compared to the arthrotomy group (mean of 3.8 days versus 6.4 days, $p < 0.0001$) [13]. The results of this study suggest that hip arthroscopy is a valid alternative to hip arthrotomy for septic arthritis of the hip joint. Similar findings were reported by another study [5].

For septic arthritis of the knee, arthroscopy tends to be the operative choice [12,13]. Again, data is lacking to support these claims. Other studies have suggested that arthrotomy may be better for septic arthritis of the shoulder and the hip joint due to the tight space in these joints to allow entry of arthroscopic instruments [10,12]. Baker et al. noted that arthroscopy can be a viable alternative as well in the shoulder and ankle joints [12]. Conversely, Peltola et al. report in their prospective randomized trial that most of the included patients in their study did not require any operative procedures beyond a diagnostic aspiration [16]. Despite the debate over the technique and necessity of surgical interventions, the literature does emphasize that early diagnosis and prompt treatment are paramount when caring for suspected septic arthritis patients [5,8,10,13].

Other studies have attempted to streamline the diagnostic approach to patients with suspected septic arthritis. Kocher et al. established a clinical algorithm in order to aid in early diagnosis of pediatric septic hips [14]. Their criteria included the inability or refusal of the patient to bear weight, history of fever (defined as an oral temperature >38.5 °C), a serum WBC count greater than 12,000 cells/mm^3 and an erythrocyte sedimentation rate (ESR) greater than 40 mm/hr [14]. Later studies found greater efficacy when incorporating CRP into this algorithm [17–19]. However, this clinical algorithm has not been fully validated across all populations and further studies must be carried out before it can be applied universally [15,20].

Despite significant heterogeneity in the literature regarding surgical indications and operative techniques for osteomyelitis and septic arthritis, there is more of a consensus on the use of CRP and ESR for aiding in diagnosis and monitoring treatment response [8,17]. CRP has been proven as an effective test for diagnosis and monitoring of response to treatment [5,8,10,16]. ESR was classically associated as a laboratory marker for osteomyelitis but has now been widely replaced by CRP [10]. The short half-life of CRP allows for more precise monitoring for efficacy of treatment. Decreasing CRP levels are indicative of treatment efficacy [8,16]. Pääkkönen et al. found that even with persistent pyrexia, decreasing CRP levels could be used to justify switching antibiotics from intravenous to oral [10]. They also report that they were able to safely discontinue antibiotics after 10 days as long as CRP levels were less than 20 mg/dL [10,16]. In circumstances when the CRP levels does not decline or continues to increase, further workup or additional interventions may be necessary as this suggests a suboptimal clinical response to the current treatment [16].

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QUESTION 2: How radical should surgery be for osteomyelitis/septic arthritis?

RECOMMENDATION: In pediatric patients with osteomyelitis/septic arthritis who require surgical intervention, aggressive debridement and copious irrigation of the infected joint is required.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 89%, Disagree: 7%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

The treatment of choice for septic arthritis in children is irrigation and debridement of the septic joint to clear the joint of bacteria and destructive enzymes and also decrease the intra-articular pressure to avoid articular cartilage damage and ischemia [1,2].

Septic arthritis of the hip joint has been posited as an emergent condition in pediatric patients often requiring open arthrotomy as soon as confirmation of the disease is made with joint aspiration [1–5].

There are a few reports that show equivalent outcome for treatment of hip septic arthritis when arthroscopy versus arthrotomy was employed [6,7]. Repeated aspirations of the hip joint under ultrasound guidance was shown to be effective in 85% of children without the need for an arthrotomy [4,8–11]. The indication for surgical treatment of septic arthritis of other joints remains controversial. Drainage of any large effusion present in joints is usually advocated. In ankle, knee and shoulder joints, arthroscopic irrigation or aspiration and lavage may be appropriate [1,3].

There is no consensus for the time, type and extent of surgical procedures in patients with osteomyelitis [1]. Surgery is recommended in the presence of subperiosteal abscess, bone necrosis or direct invasion of the growth plate that may be seen in magnetic resonance imaging (MRI) images [2]. It is also indicated if a patient does not respond to antibiotic therapy, based on clinical examination, laboratory indices and imaging studies (particularly MRI) [1].

The decision to drain a subperiosteal collection seen on ultrasound cannot be based purely on the size of collection but needs to take into account the clinical findings of the patient and the response to antibiotic therapy [12–14].

During surgical intervention often a cortical window is created [1,15], but the optimal treatment for sub-periosteal abscess remains controversial in terms of whether or not a corticotomy or intramedullary drainage needs to be performed [1,16,17]. There is limited evidence to suggest that subperiosteal drainage alone is adequate management for a subperiosteal abscess [18–20].

Montgomery et al. [21] in a retrospective comparative study demonstrated that in patients with subperiosteal abscess, intramedullary drainage significantly decreased the need for repeat surgery. Another factor to consider when dealing with pediatric patients with septic arthritis is the virulence of the infective organism. In patients with methicillin-resistant *Staphylococcus aureus* (MRSA) infections, more aggressive surgical intervention is warranted, as these patients are at risk of relapse and often need repeated surgeries [15,22–24].

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QUESTION 3: Is there a role for arthroscopic washout in children with septic arthritis?

RECOMMENDATION: Yes. Arthroscopy is a useful tool in the treatment of septic arthritis in children.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 83%, Disagree: 10%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Early diagnosis of septic arthritis (SA) in the pediatric age group is essential in order to avoid adverse sequelae associated with delayed SA, such as osteonecrosis, chondrolysis, relapse or recurrent SA and sepsis, and is more important than the type of drainage[1–3].

For decades, the prevailing treatment of pediatric SA after early diagnosis was open arthrotomy, irrigation and debridement [2,4,5]. The optimal technique for drainage is controversial between needle aspiration, arthrotomy or arthroscopy. Arthroscopic drainage in adults with knee SA is the accepted treatment of choice, as functional outcome and success of treatment is better using this method of treatment [6,7]. Arthroscopic treatment of SA in pediatric patients is defined as a successful option for septic arthritis of the hip, knee, ankle and shoulder in children [8,9].

Despite concern about traction in septic hips during the infection process, several studies have demonstrated its safety [10–13].

Kim et al. and Chung et al. reported good results of hip arthroscopy utilization in SA [11,14,15]. In a prospective comparative study on hip SA, children treated arthroscopically had better functional outcomes (90% excellent vs. 70% in open arthrotomy group), significantly shorter hospital stays and a lower rate of scarring due to the less invasive nature [16].

A recent study with a 2.5-year follow-up supported these results [9]. In these reports, all repeated drainage was done arthroscopically, and it was safe for even very young children.

In a 7-year follow-up comparative study of arthroscopic washout vs. open arthrotomy, Johns et al. reported reduced rates of repeat drainage, earlier knee range of motion and weight-bearing in the arthroscopic arm; however, these trends did not reach a statistically significant difference [17].

In a series of 76 children with arthroscopically-treated septic arthritis, a combination of arthroscopic lavage and antibiotic therapy successfully eradicated infection in 91% patients, and open revision was only required in 4% of these cases [18].

In summary, arthroscopic washout is a useful procedure for the treatment of pediatric septic arthritis, but the evidence is weaker than in the adult literature. Limited sample size and an absence of randomized clinical trials are evident in both knee and hip SA in the pediatric setting. Thus, there is no definitive evidence to support arthroscopic washout over open arthrotomy in children.

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QUESTION 4: Should the length of antibiotic usage be different for a primary septic arthritis (SA) versus osteomyelitis (OM)?

RECOMMENDATION: Although there is a tendency towards prescribing a longer course of antibiotics in pediatric patients with OM compared to primary SA, this practice is not based on conclusive evidence.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 2%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

For decades, it has been believed that a prolonged course of antibiotic therapy (four to six weeks) is necessary to improve long-term outcomes when treating OM and SA in children [1–3]. In recent years, the efficacy of prescribing a prolonged course of antibiotics in the treatment of SA has begun to be questioned. Recent studies, including clinical trials, have demonstrated that a shorter duration (less than one week) of antibiotic therapy, in particular intravenous antibiotics, is effective in treating selective groups of pediatric patients with musculoskeletal infection while reducing length of stay, complications and healthcare costs [4–9].

Jagodzinski et al. demonstrated in a prospective study that three to five days of parenteral antibiotic therapy was sufficient for treating osteoarticular infection in children [10]. However, the Infectious Diseases Society of America (IDSA) currently recommends

a six-week course of antibiotics are administered to children with methicillin-resistant *Staphylococcus aureus* (MRSA) infection of the musculoskeletal system [11].

There is also no consensus or published studies about the optimal transition time from intravenous to oral antibiotic therapy in pediatric osteoarticular infection. There is, however, agreement in clinical practice that a transition from parenteral to oral antibiotics should occur when clinical signs and serum laboratory markers improve [12–14].

An extensive search of the literature revealed 33 retrospective observational studies related to management of pediatric musculoskeletal infections. The median length of antibiotic usage in these studies ranged from two to five weeks for SA patients and three to eight weeks for OM patients. Many of these studies had small sample sizes, short follow-up duration and heterogeneous patient populations, thus precluding meaningful comparison. In studies analyzing both SA and OM populations, a longer duration of antibiotics was consistently reported for OM patients [15–17].

There have been no high-level studies examining the appropriate length of antibiotic treatment for pediatric patients with SA vs. OM. In the absence of such concrete evidence, it remains unclear if the length of antibiotic treatment should be different for primary SA vs. OM. From the results of review of the available literature, it appears that uncomplicated cases of SA may be treated with a shorter duration of antibiotics than OM. This aligns with current guidelines from the European Society for Pediatric Infectious Diseases as well as the Australasian Society for Infectious Diseases, which both recommend an average of two to three weeks of antibiotics in SA and three to four weeks of antibiotics in OM [18,19]. Australian Therapeutic Guidelines suggest similar durations of three weeks in SA and three weeks minimum in OM [20,21]. However, length of antibiotic usage should be evaluated individually and guided by clinical response. There is a paucity of data on antibiotic duration in neonates, immunocompromised patients, patients with bone abscesses, those with chronic OM and infections caused by MRSA. The optimal length of therapy in these groups is yet to be defined. Thus, larger prospective randomized clinical trials of methodological rigor are required.

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QUESTION 5: Do steroids have a chondroprotective effect in children with septic arthritis (SA)?

RECOMMENDATION: Based on available pre-clinical and clinical studies it appears that the concurrent use of corticosteroids and antibiotics may have a protective role in the management of SA in the pediatric patient population.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 58%, Disagree: 20%, Abstain: 22% (Simple Majority, NO Consensus)

RATIONALE

SA can lead to severe joint disabilities in about 30% of affected children. These disabilities include restriction of bone growth, chondral destruction, stiffness, pathologic fracture, limb-length discrepancy, subluxation and chronic dislocation of the joint [1,2].

The processes leading to these sequelae are thought to be due more to inflammatory responses than direct damage caused by

microorganisms. Rapid proliferation of bacteria within the joint space activates a cascade of pro-inflammatory cytokines including, interleukin (IL)-1 beta, IL-6, IL-17 and tumor necrosis factor (TNF)-α [3]. These cytokines, in conjunction with the TNF receptor-ligand family receptor activator of nuclear factor kappa-B ligand (RANKL), are believed to play a critical role in the activation and proliferation of osteoclasts, leading to bone resorption. Specifically, the interaction between RANKL and its receptor, RANK, has been shown to be required for osteoclast differentiation. Expression dysregulation of these factors in SA can lead to significant osteolysis [4,5]. In addition, increased synovial fluid and joint effusion in SA can obstruct blood supply of the joint, leading to chondrocyte necrosis, even during the early hours of infection [6].

Glucocorticoids have an established role in suppressing the release of proinflammatory cytokines in almost all acute or chronic diseases [7]. They are used to control inflammatory conditions affecting the joint, such as rheumatoid arthritis and ankylosing spondylitis. Corticosteroids also reduce the production of proteolytic enzymes, such as elastase, collagenase and synovial matrix metallopeptidase-1 (MMP-1), thereby preventing the chondral degradation process [7,8]. Despite the use of corticosteroids in inflammatory conditions, they are avoided in patients who have infections due to their immunosuppressive effect and their potential to exacerbate infection. However, recent evidence suggests that the concurrent use of corticosteroids with antibiotics improved the care of patients with central nervous system infections, pneumonia, upper urinary tract infection and sepsis [9–12].

The chondroprotective effect of glucocorticoids was investigated by two separate studies in 1996. Stricker et al. and Sakiniene et al. investigated the chondroprotective effect of corticosteroids on the course of SA [13,14]. Both studies utilized animal models to investigate if the administration of glucocorticoids had any influence on the levels of circulating inflammatory mediators. Stricker et al. employed the rabbit model and Sakiniene et al. utilized a mouse model to demonstrate that the administration of glucocorticoids resulted in improvement in symptoms in the animals and a significant decrease in serum levels of inflammatory cytokines at two weeks.

Extensive search of the literature revealed four clinical studies that relate to this subject (Table 1). These studies consist of two double-blinded randomized control trials, one non-randomized clinical trial and one retrospective study [15–18]. The findings of the studies are summarized in Table 1. All studies demonstrate improvements in clinical symptoms, length of hospital stay, reduced use of antibiotics or faster return to normal of serum inflammatory markers, such as C-reactive protein (CRP). In 2015 a meta-analysis was published regarding the use of corticosteroids in SA that included three of the aforementioned studies [19]. The finding of the meta-analysis was that the use of corticosteroids combined with antibiotics resulted in an improvement in the outcome of management of SA in children.

Despite the availability of evidence to support the use of corticosteroids in pediatric patients with SA, some concerns still remain. These concerns are:

1. The studies do not specifically seek adverse effects associated with the administration of corticosteroids.
2. Long term follow-up on patients receiving steroids is not available.
3. Total participant number of these studies is low.
4. Optimum dose, duration and route of prescription of corticosteroids is not clear yet.

TABLE 1. Summary of studies

Author (Year)	Study Design	Participants	Treatment Protocol	Results (Follow-up)
Odio et al. (2003) [15]	Randomised clinical trial	100 children	4 days of dexamethasone + AB	Significant decrease of joint dysfunction (12m) Quicker normalization of CRP Earlier symptoms relief Decreased IV antibiotics days
Harel et al. (2011) [16]	Randomised clinical trial	49 children	4 days of dexamethasone + AB	Significant decrease of joint dysfunction (12m) Became afebrile earlier Quicker normalization of CRP Decreased IV antibiotics days Decreased hospitalization
Arti et al. (2014) [17]	Non-randomized clinical trial	60 children	4 days of dexamethasone + AB	Decreased hospitalization Better final ROM Decreased local sign of inflammation Higher ESR reduction rate
Fogel et al. (2015) [18]	Retrospective	116 children	Few days of dexamethasone + AB	Rapid clinical improvement Quicker normalization of CRP Decreased IV antibiotics days Decreased hospitalization

The aforementioned concerns are important enough to justify the need for larger scale prospective studies with a longer follow-up that examine the benefits as well as the potential adverse effects of corticosteroids administered to pediatric patients with SA.

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QUESTION 6: What is the optimal management of septic arthritis/osteomyelitis (SA/OM) caused by methicillin-resistant *Staphylococcus aureus* (MRSA)?

RECOMMENDATION: Patients with MRSA infection should be started on an antibiotic regimen, such as vancomycin, intravenously followed by linezolid, which is effective against this organism. Early consideration for surgical treatment and close monitoring is essential in pediatric patients with musculoskeletal MRSA infection to reduce the high prevalence of complications and late sequelae that are often seen.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 85%, Disagree: 11%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE:

In past decade, the prevalence of MRSA in SA and acute OM has dramatically risen between 3- to 10-fold [1–3]. Compared to methicillin-susceptible *Staphylococcus aureus* (MSSA) infections, patients with MRSA have more extensive areas of soft tissue destruction, more rapid spread of infection and experience higher mortality rates [2–4]. The course of treatment of these patients is also protracted with a longer length of hospital stay, need for surgical intervention and an increased risk of complications, such as persistent bacteremia, deep vein thrombosis, pulmonary embolus, pathologic fractures and other long-term sequelae [1,2,5–10].

The severity of MRSA infections may be related to virulence factors, such as Panton-Valentine Leukocidin (PVL) found in many MRSA strains [11,12]. MRSA strains may also contain specific virulence factors that are linked to increased soft tissue destruction, such as α-hemolysin and α-type phenol-soluble modulin [3].

Pediatric patients with MRSA infections are more systematically unwell with higher temperatures and increased tachycardia. In addition, they present with even higher leukocytosis (or absolute neutrophil count), greater elevations in erythrocyte sedimentation rate and C-reactive protein but lower hematocrit values [5,7,10,13].

Commencing appropriate empiric antibiotics in these patients is paramount to improve outcomes. Children with suspected MRSA SA or OM should be started on intravenous vancomycin or clindamycin. Daptomycin or Linezolid are alternatives for the treatment of MRSA infections in children. The duration of therapy should be individualized based on the response to treatment. A minimum course of three to four weeks for SA and four to six weeks of antibiotics for OM is recommended [4,14].

Cultures should ideally be obtained before initiating antibiotics in patients with musculoskeletal infection, especially if MRSA is suspected. Aspiration of the affected joint and obtaining blood cultures helps isolate the infective organism and should be part of the initial work up of these patients [14,15]. New diagnostic methods, such as real time polymerase chain reaction (PCR), may be useful in the rapid identification of MRSA or other infective organisms [5].

Appropriate imaging, such as magnetic resonance imaging (MRI), should also be part of the work up since this allows for localization of the infection and determination of the extent of disease. MRI may also help with surgical planning to ensure a more thorough debridement and decompression of infected areas [10,15,16].

Images may also reveal subperiosteal abscess formation or the presence of SA in the hip. The presence of such findings lead to the need for early surgical intervention since antibiotics cannot typically penetrate large abscess cavities. Compared to MSSA infections, MRSA infections are more invasive and have a higher rates of abscess formation. Thus, they require surgical intervention more frequently and a higher number of repeat procedures [5].

Aggressive surgical management during the initial procedure, involving opening a surgical window and intramedullary irrigation, is necessary to prevent the need for subsequent reoperation. Close monitoring of patients is critical to prevent complications and reduces long-term sequelae. Patients who fail to respond to antibiotics should undergo prompt surgical interventions. Repeat imaging should also be considered in patients who are not responding to treatment in order to determine persistent infection and assess the extent of bony and soft tissue involvement [6,10,11,14,16].

In summary, MRSA infections of the musculoskeletal system in children may have serious complications. They require early administration of antibiotics and may necessitate multiple surgical interventions. These patients often have a protracted hospital course and require vigilant monitoring to minimize the risk of complications.

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QUESTION 7: What is the best management for mycobacterium tuberculosis (TB) of the musculoskeletal system in children?

RECOMMENDATION: Mycobacterium TB periprosthetic joint infection (PJI) must be treated in collaboration with an infectious disease specialist, noting that the duration of treatment (minimum six months and up to two years) and the type of antimicrobials (usually a combination of four drugs) is determined based on the resistance profile of the pathogen.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 86%, Disagree: 2%, Abstain: 12% (Super Majority, Strong Consensus)

RATIONALE

There is an agreement that anti-TB medications can eradicate most of the bacilli and prevent both relapse and drug resistance. The current recommendation for treatment length of extra-pulmonary TB in children is six months. However, these recommendations do not apply to osteoarticular infections and meningitis. Almost all available guidelines strongly recommend 12 months of anti-TB treatment for osteoarticular TB [1–5].

The recommended regimen for children with suspected or confirmed osteoarticular TB is a four-drug regimen consisting of Isoniazid (INH), Rifampin (RIF), Pyrazinamide (PZA) and Ethambutol (EMB) for 2 months, followed by a two-drug regimen of Isoniazid and Rifampin (HR) for 10 months [6].

There is limited literature that describes how to treat children with drug-resistant TB. For mono-drug resistance to either Isoniazid or Rifampicin, the recommendation is for 6-9 months of a three-drug regimen consisting of the other susceptible antibiotics from

TABLE 1. Recommendations for treatment of resistant TB in pediatrics

	Initial Phase	Maintenance Phase
INH-monoresistance TB	RIF + PZA + EMB (2 months)	RIF + PZA + EMB (4-7 months)
RIF-monoresistance TB	INH+ PZA + EMB + FQN (2 months)	INH + EMB + FQN (10-16 months)

INH, Isoniazid; EMB, Ethambutol; RIF, Rifampicin; PZA, Pyrazinamide; FQN, Fluoroquinolones; TB, Tuberculosis

the conventional four-drug regimen (Table 1) [3,7,8]. For multi-drug resistant (MDR) TB, all guidelines recommend a longer treatment period of up to 24 months with all four anti-TB drugs [3,7,9]. Evaluation of the organism's drug susceptibility profile should also be conducted [3,7,9].

While some authors have reported favorable results with chemotherapy and non-operative splinting of the affected joint(s), others have recommended debridement of focal bony involvement and arthroscopic or open synovectomy to decrease the overall bioburden of infected material [10,11].

Arthrodesis, especially of the hip joint, may be an option in the event of severe destruction of the joint secondary to infection [12]. Orthopaedic interventions in spinal TB may occasionally be recommended to prevent deformity of the spine in pediatric patients. These procedures may include surgical intervention, application of a brace or cast in addition to standard chemotherapy. Proper immobilization of the growing spine in pediatric patients may help achieve a solid fusion without surgical procedures.

Surgical intervention is reserved for patients with formation of a large anterior column abscess, severe kyphotic deformity or progressive spinal deformity despite chemotherapy [13,14].

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QUESTION 8: What is the role of host gene expression and severity of acute osteoarticular infection in children, especially methicillin-resistant *Staphylococcus aureus* (*S. aureus*), or MRSA, infection?

RECOMMENDATION: Unknown. The limited literature available suggests altered host gene transcription related to the balance of the body's adaptive and innate immune responses may increase pediatric patients' susceptibility to severe osteoarticular infection, particularly in cases of MRSA. However, much more investigation is needed to determine which genes are most useful and how they can be utilized to help physicians anticipate the course of infection in a given patient.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 75%, Disagree: 3%, Abstain: 22% (Super Majority, Strong Consensus)

RATIONALE

The severity of osteoarticular infection in otherwise healthy children varies greatly, even in the setting of infection by the same pathogen. Some pediatric patients experience a mild course that allows them to be discharged after a few days of hospital admission with antibiotic therapy. Other patients experience a protracted course and require major surgical intervention as well as intensive care management [1–3]. The contribution of genetic mechanisms to this wide range of clinical manifestations has been investigated to a limited extent. A similar diversity in illness severity has been observed in neoplastic and rheumatologic disorders, where there is evidence that ribonucleic acid expression plays a role in the presentation of these conditions [4–6]. Chaussabel et al. used gene expression microarrays in patients with seven autoimmune-related conditions and identified transcriptional changes ("diagnostic signatures") that could be used to distinguish between these respective conditions [7]. Identifying a parallel set of transcriptional diagnostic indicators for the severity of osteoarticular infection may enhance the ability of physicians to treat this condition.

S. aureus is one of the leading pathogens causing hospital-acquired infection and MRSA infection is associated with over 6,000 deaths/year in the United States [8]. In a series of 99 children hospitalized with *S. aureus* infection, investigators used microarray analysis to characterize the transcriptional profiles in whole blood. Significant heterogeneity was observed in host signatures and transcriptional changes were identified. Furthermore, this heterogeneity was found to be associated with a more severe course of disease. Overall, patients with invasive *S. aureus* infection had an exaggerated expression of genes associated with the innate immune response and a diminished expression of adaptive immunity [9].

Ardura et al. conducted a study comparing gene expression in peripheral blood monocyte cells (PBMC) between 53 children with invasive *S. aureus* infection and 24 healthy children. Analysis of PBMC gene expression showed that patients with invasive *S. aureus* had lower numbers of central memory CD4+ and CD8+ T-cells and increased numbers of CD14+ monocytes versus healthy controls [10]. Ramilo et al. compared the immune system response in patients with *Escherichia coli* infection versus those with *S. aureus* infection. Their findings support the specific pattern described by Ardura et al. They found that patients with *S. aureus* infection had altered host gene expression associated with their adaptive immune response [11]. Gaviria-Agudelo et al. reported on a cohort of 12 pediatric patients with acute hematogenous osteomyelitis caused by MRSA, and they identified specific genes which correlated with the severity of disease in the early hospitalization period. Among the five distinct genes that were identified, three were up-regulated (P2RX1, SORT1, RETN) and two were down-regulated (LOC641788, STAT 4). STAT4 down-regulation showed the strongest correlation with disease severity [12].

While these findings provide some initial evidence for the role of host gene expression in the severity of acute osteoarticular infection in children, the literature on this topic remains sparse. Further studies are needed to examine this connection, particularly studies with larger sample sizes. An enhanced understanding of host gene expression patterns and the transcriptome in osteoarticular infection could enable physicians to better anticipate the risk of developing chronic osteomyelitis and, ultimately, facilitate personalized patient management strategies.

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