PART I

GENERAL ASSEMBLY

Continued...

Prevention

1.1. PREVENTION: HOST RELATED, LOCAL FACTORS

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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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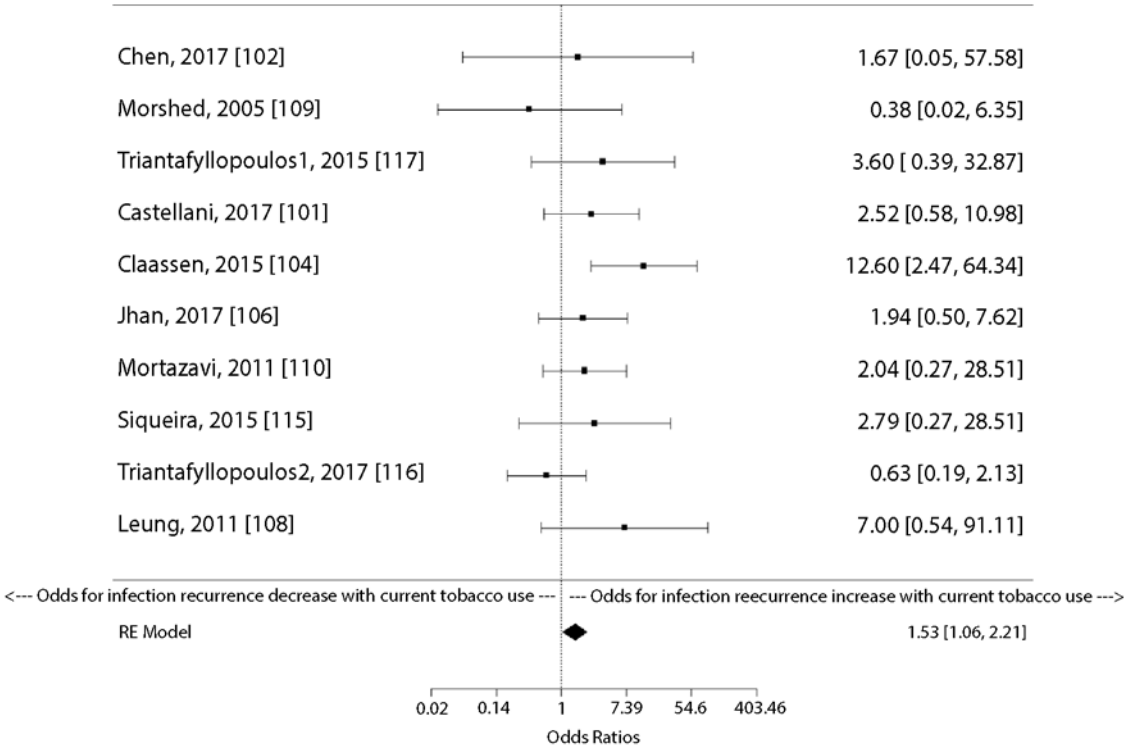

FIGURE 1. Odds ratios for infection recurrence with current tobacco use versus no tobacco use.

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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

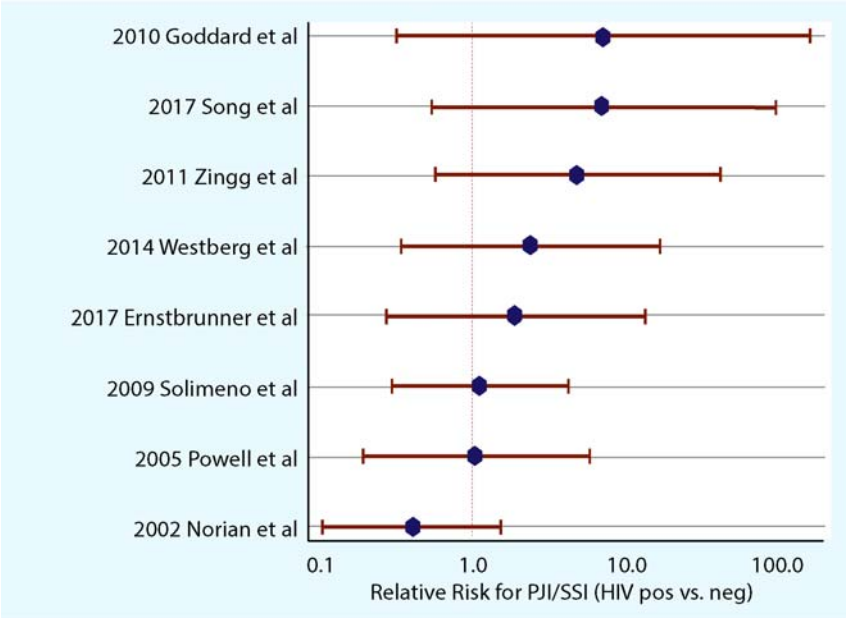

FIGURE 1. Forest plot of relative risk of PJI/SSI in HIV-infected hemophiliacs vs. HIV-negative hemophiliacs.

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

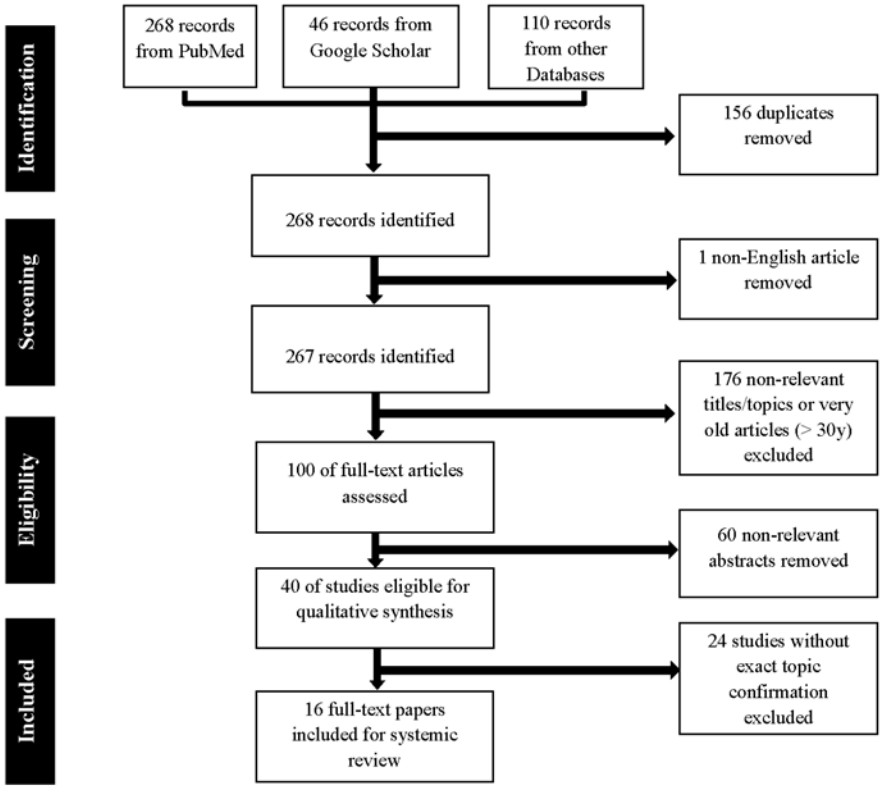

FIGURE 1. PRISMA Flowchart showing the identification of relevant studies during the review process.

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

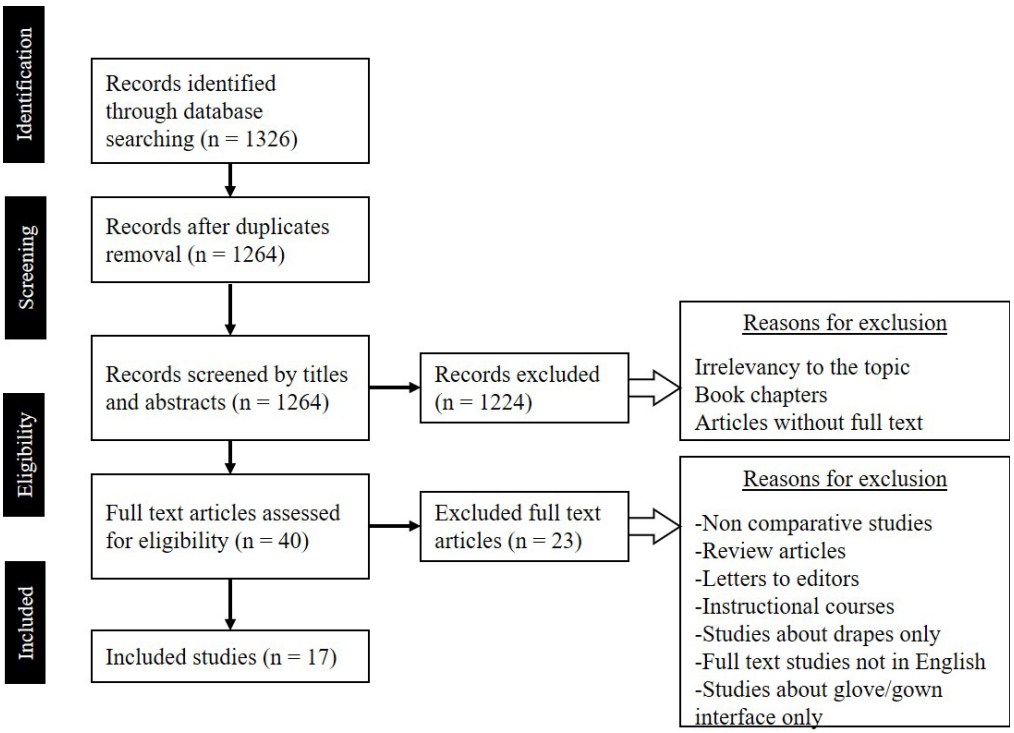

FIGURE 1. Study selection for the systematic review.

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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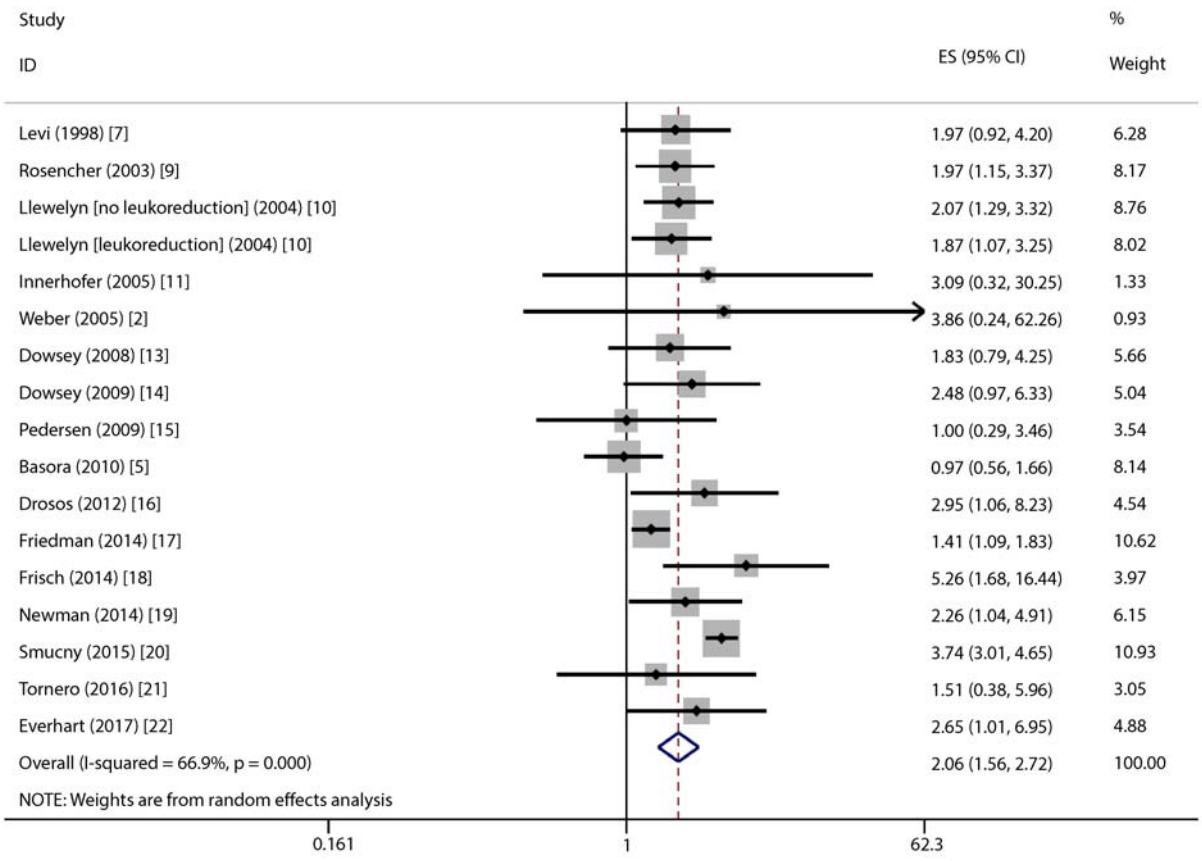

FIGURE 1. Forest plot comparing allogeneic transfusion to no transfusion. (CI, confidence interval; ES, effect size).

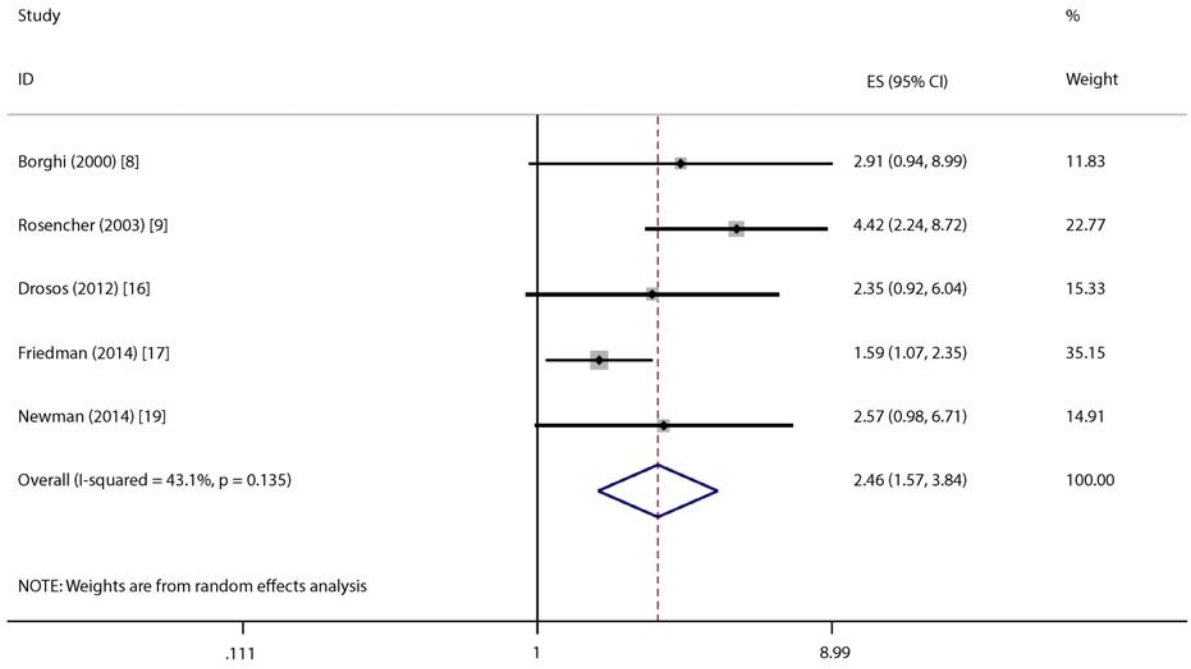

FIGURE 2. Forest plot comparing allogeneic transfusion to autologous transfusion. (CI, confidence interval; ES, effect size).

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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.