PART II

HIP AND KNEE

Continued...

Prevention

1.1. PREVENTION: HOST RELATED

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QUESTION 1: What are the absolute and relative contraindications to elective primary total joint arthroplasty (TJA), with respect to surgical site infection (SSI) and periprosthetic joint infection (PJI) risk?

RECOMMENDATION: Elective joint arthroplasty is contraindicated in patients with an infectious lesion in the ipsilateral extremity, until the infection is resolved. TJA needs to be deferred in patients with uncontrolled conditions such as diabetes, malnutrition, chronic kidney disease, as well as other diseases that are known to increase the risks of SSIs/PJIs.

LEVEL OF EVIDENCE: Strong

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

RATIONALE

Immunosuppression and Rheumatoid Arthritis (RA) (Relative Modifiable Risk Factors (MRF))

Evidence Strength: Moderate

Current studies evaluating the risks of PJIs in immunosuppressed patients have primarily been grounded in transplant patients (discussed in later sections), and those receiving biologics or non-biologic disease modifying anti-rheumatic drugs (DMARDs). In a Japanese study by Momohara et al., the risk for post-TJA SSI due to biologic DMARDs was compared against that of non-biologic DMARDs in RA patients [1]. Of note, non-biologic DMARDs were continued throughout the perioperative period, but biologic DMARDs were withheld in concordance with the British Society for Rheumatology and Japanese College of Rheumatology guidelines (~2 to 4 weeks based on half-life). The odds ratio (OR) for SSIs with biologic DMARDs was 5.69 (95% confidence interval (CI) 2.07-15.61). Furthermore, multiple logistic regression analysis found tumor necrosis factor-α blocker therapy to be the most potent of the biologics, with infliximab conferring a 9.8 greater odds (OR 2.41-39.82) and etanercept conferring 9.16 greater odds (95% CI 2.77-30.25) for SSIs. The only other significant risk factor for increased SSIs was RA disease duration (OR 14.5; 95% CI 8.9–21.0). A separate Japanese hospital surveillance study also demonstrated a smaller, but significant increase in SSIs with biologic DMARDs when compared to non-biologic DMARDs (OR 2.12; 95% CI 1.48–3.03) [2].

Conversely, a Danish database study comparing biologic versus non-biologic DMARD treated TJA candidates found no significant differences in PJI rates (adjusted hazards ratio 1.61; 95% CI 0.70-3.69) [3]. Furthermore, glucocorticoid exposure within 90-days of surgery was found to increase the 1-year risk for PJIs (OR 2.31; 95% CI 1.09 to 4.89). Lastly, one-year PJI risk was also elevated in RA patients when compared to osteoarthritis patients (OR 1.59; 95% CI 1.23-2.04).

The American College of Rheumatology (ACR) and American College of Hip and Knee Surgeons (AAHKS) have recently developed guidelines with regards to biologic and non-biologic drug management in the perioperative period [4]. Current guidelines indicate biologic DMARDs are to be discontinued in the perioperative period based on medication half-lifes. However, discontinuation may still not deter the risks conferred. In general, traditional, nonbiologic DMARDs can be continued throughout the perioperative period.

Intra-articular Injections (Modifiable)

Evidence Strength: Strong

In a matched cohort database study by Cancienne et al., patients receiving intra-articular corticosteroid injections of the knee were separated into three cohorts based on the last injection prior to surgery: 0 to 3 months, 3 to 6 months and 6 to 12 months. Matched controls were selected based on the absence of any previous intra-articular injections. Patients receiving intra-articular steroids 0 to 3 months before surgery demonstrated an increased risk for infection at 3 months (OR 2.0; 95% CI 1.6-2.5; 2.60% vs. 1.33%) and 6 months (OR 1.5; 95% CI 1.2-1.8; 3.41% vs. 2.34%) postoperatively. For patients receiving corticosteroids more than 3 months preoperatively, no increase in postoperative PJI was observed. A similar database study of 173,958 THAs by Schairer et al. showed intra-articular corticosteroid injections 0 to 3 months preoperatively increased the risk of infection 0 to 3 months (Hazard Ratio (HR) 1.52), 3 to 6 months (HR 1.46) and 6 to 12 months (HR 1.39) postoperatively [5]. Similar to the findings from Cacienne et al., it was reported that steroids injected greater than three months preoperatively did not increase postoperative PJI risks.

The quantity of intra-articular steroid injections within one year of surgery may also play a role in PJIs. Chambers et al. reported increased infection rates in patients who received two or more intra-articular steroid injections (OR 3.30; 2.0% vs. 6.6%) when compared to those who only received one. Like the studies performed by Cancienne et al. and Schairer et al., viscosupplementation patients were excluded from the study.

Current systematic reviews and meta-analyses have attempted to better define the effects of intra-articular injections, but a paucity of prospective studies, randomized-control trials and highly variable study designs have led to highly confounded and poorly defined results [6–9]. Moreover, with PJI rates of approximately 3% in total knee arthroplasty (TKA) [10] and 0.4-2.2% in total hip arthroplasty (THA) [11,12], current studies are reported to be too underpowered to detect the differences in PJI rates.

There is strong evidence that surgery should be absolutely delayed for a minimum of three months following intra-articular steroid injections. Surgeons may also consider intra-articular injections of the knee within three months to one year a potential relative contraindication. However, future large cohort or randomized control trials are required to assess the true risks. Evidence regarding viscosupplementation is unavailable.

Body Mass Index (BMI) ≤ 20 (Modifiable)

Evidence Strength: Moderate

In a case-control study of 27 patients by Manrique et al., underweight patients (BMI <18.5 kg/m^2) suffered from an increased risk for SSIs (11.1% vs. 0.0%). Conversely, in a database study of 4,665 TJAs by Anoushiravani et al., patients who are underweight (BMI ≤ 19 kg/m^2) were at reduced risks for PJIs (OR 0.23; 95% CI 0.09-0.61) [13]. Similarly, when underweight patients were compared to obese patients, no differences in infection rates were observed [14]. Current evidence for or against PJIs in underweight patients are equivocal; however, due to the multitude of complications associated with underweight patients, TJA is relatively contraindicated, and medical optimization should precede TJA.

Obesity (Modifiable)

Evidence Strength: Strong

In a retrospective database study by Werner et al., postoperative outcomes of 891,567 patients undergoing THA were stratified into four distinct cohorts: non-obese (BMI < 30 kg/m^2), obese (BMI 30-40 kg/m^2), morbidly obese (BMI 40-50 kg/m^2) and super-obese (BMI > 50 kg/m^2) [15]. The risks of SSIs increased with increasing BMI. SSI rates were noted to be 0.8% in the non-obese, 2.6% in the obese, 5.2% in the morbidly obese and 12.4% in the super-obese. In a study of 71,599 cases by Fu et al., wound complications (superficial infections, deep surgical site infections, organ space surgical site infections or wound dehiscences) were also observed to positively correlate with BMI, with 0.8% of non-obese patients experiencing wound complications, 0.9% in class 1 obesity, 1.0% in class 2 obesity and 1.7% in class 3 obesity [16]. In addition, patients diagnosed with malnutrition were two times more likely to have wound complications (2.0% vs. 1.0%). Hypothyroidism should also be evaluated in this population, as new studies indicate a potential causal link between the two disease states and PJI [17,18]. These findings of increased SSIs with obesity have been supported by several meta-analyses [19–21]. Current management guidelines indicate weight loss is helpful in reducing PJIs in this patient population. Hence, obesity is considered a relative contraindication while morbid obesity serves as an absolute contraindication. However, the current approach to weight loss protocols is highly controversial, with no absolute guidelines for which methodology (e.g., diet/exercise vs. medically prescribed very low-calorie diets vs. bariatric surgery) is superior.

Bariatric Surgery (Non-modifiable)

Evidence Strength: Strong

Studies regarding the effect of pre-TJA bariatric surgery remain equivocal. In a matched cohort study by Inacio et al., bariatric surgery did not result in significantly lower rates of 1-year deep or 30-day superficial infections when compared among patients with bariatric surgery > 2 years prior to TJA (superficial 0%; deep 1.5%), those with bariatric surgery within 2 years of TJA (superficial 2.0%; deep 1.0%) and obese patients without bariatric surgery (superficial 1.2%; deep 0.5%) [22]. In a study by Watts et al., bariatric patients experienced a non-significant trend towards lower infection rates compared to controls matched by BMI (HR 1.3; 95% CI 0.8-20.3) [23]. It is suspected that in patients undergoing bariatric surgery prior to TJA, the risks for PJIs are reduced due to decreasing BMIs, but is offset by the increased risk for malnutrition. Improved patient stratification (e.g., malnutrition workup) may allow for better risk appraisal of these patients preoperatively.

Malnutrition (Modifiable)

Evidence Strength: Strong

The estimated prevalence of malnutrition in TJA patients ranges from 27 to 50% [24–26]. Malnutrition patients can be described using a variety of markers including serum albumin < 3.5 g/dL, total lymphocyte count < 1,500/mm^3, and/or transferrin < 200 mg/dL [27,28]. Multiple reviews have supported the claims that the degree of malnutrition correlates with an increased risk of impaired wound healing, persistent wound drainage, PJI and low success rates of the initial irrigation and debridement (I&D) [29–35]. In a small cohort study by Lavernia et al., it was reported that 4.54% of patients with an albumin < 3.5 g/dL developed a deep infection versus 2.06% in controls [36]. Many other studies have confirmed malnutrition to be a significant risk factor for prolonged hospitalization and postoperative complications, particularly SSIs and PJIs [33,37]. In a prospective study of 779 primary TJA patients, Kamath et al. found the incidence of preoperative albumin < 3.5 g/dL to be 15% [38]. In a separate, matched cohort study, malnutrition (albumin < 3.5 g/dL) was determined to be an independent risk factor for PJIs (adjusted OR 3.00, 95% CI 1.56 to 5.75) [39]. In a propensity-matched, retrospective, American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database analysis of 34,800 TKA patients with preoperative albumin levels, Fu et al. reported that preoperative hypoalbuminemia was a strong predictor for multiple complications (OR 1.78, 95% CI 1.20 to 2.64) [16]. A retrospective cohort-control study of 49,603 TJAs reported the prevalence of hypoalbuminemia to be 4%, placing patients at a significantly higher risk of SSIs (risk rate (RR) 2.0, 95% CI 1.5 to 2.8) [40].

In a retrospective cohort, Jaberi et al. confirmed that malnutritioned TJA patients were more likely to develop a deep infection and require further treatment with I&D [28]. Of these I&D patients, 35% continued to fail. Bohl et al. found that patients with hypoalbuminemia were three times more likely to have an indication of sepsis for revision arthroplasty (RR 3.8, 95% CI 3.4 to 4.3), and twice as likely to develop PJIs within 30 days of revision for aseptic indications (RR 2.1, 95% CI 1.2 to 3.5) [41]. A retrospective cohort study of 501 revision TJAs for PJIs noted the incidence of at least one laboratory parameter suggestive of malnutrition was 51% (OR 2.3, 95% CI 1.5 to 3.5) [32]. After multivariate analysis, Yi et al. found that malnutrition was a significant risk factor for chronic septic failures (OR 2.131, 95% CI 1.294 to 3.512) and acute PJIs complicating aseptic revision arthroplasty (OR 5.858, 95% CI 1.317 to 26.057). Severely malnutritioned patients are at

a significantly increased risk of PJIs/SSIs after primary TJA, and experience even more dramatic rates of failure and infection in revision procedures.

Malnutrition is therefore a relative contraindication for TJA. However, current guidelines recommending which patient populations to screen are currently absent. Severe malnutrition (serum albumin < 3 g/dL), however, should be an absolute contraindication.

Diabetes Mellitus (Modifiable)

Evidence Strength: Strong

Outcomes regarding PJIs in diabetic patients have been controversial. In a retrospective cohort study of 56,216 knees, the diagnosis of diabetes was reported to confer a 1.28 (HR; 95% CI 1.03 to 1.60) greater risk for PJIs, when compared to non-diabetic controls [42]. In a Chinese study of 1,133 TKAs by Lee et al., diabetes was reported to be associated with a 6-fold (OR 6.07; 95% CI 1.43-25.75) increased risk for PJI when compared with unmatched controls [43]. In a separate study based on Chinese patients, Wu et al. showed an adjusted risk for PJIs of 5.47 (95% CI: 1.77 to 16.97) over controls. Several metanalyses have also reported a significantly elevated rate of PJIs within the diabetic population [19,42,44–48].

Conversely, in a high-quality study utilizing the Mayo Clinic Total Joint Registry, diabetes was reported not to be a risk factor for PJIs (HR 1.23; 95% CI 0.87 to 1.74) when confounding variables were appropriately adjusted for age, gender, BMI, type of surgery (THA vs. TKA), American Society of Anethesiolgists (ASA) score and operative time [49]. A separate high-quality retrospective database study by Martinez-Huedo et al. also demonstrated no substantial increases in PJIs in diabetic patients undergoing THAs (0.46 vs. 0.44%) or TKAs (0.24 vs. 0.24%) [50]. Similar to the Mayo Clinic Joint Registry report, this study extensively matched patient cohorts by variables including: year of surgery, age, sex and all of the comorbidities listed in the modified Elixhauser Comorbidity Index. Together, they indicate that diabetes may not be the primary driver of postoperative PJIs. Instead, confounding variables such as diabetic end-organ damage (e.g., chronic kidney disease, vascular disease, etc.), may be the underlying cause for PJIs in this population.

Studies regarding the utility of perioperative glucose and preoperative hemoglobin A1c (HbA1c) monitoring have also been highly heterogeneous [49,51–56]. In the Mayo Clinic Joint Registry study, after adjusting only for age and gender, perioperative glucose (+/-1 day/week) and preoperative HbA1c monitoring were not found to correlate with postoperative PJIs [49]. In a study by Iorio et al., HbA1c was not significantly different between infected diabetic (HbA1c mean 6.2%; range 5.1 to 11.1%) and nondiabetic (HbA1c mean 6.92%; range 4.7 to 15.1%) TJA patients. Chrastil et al. showed a significant increase in PJIs when evaluating maximum perioperative glucose, particularly with a cutoff of ≥ 194 mg/dL (HR 1.44; 95% CI 1.10 to 1.89), but reported no increase in PJIs for patients with HbA1c > 7% (HR 0.86; 95% CI 0.68 to 1.1) [53]. However, when graphed, an evident inflection point for increased PJIs appeared when HbA1c levels rose above approximately 8 to 9%. Similarly, serum glucose demonstrated an overt increase in infection rates when glucose levels rose above ~200 mg/dL. A meta-analysis study by Shohat et al. only showed non-significant trends for increased SSIs when correlating PJIs with HbA1c levels in a pooled OR of 1.49 (95% CI 0.94 to 2.37). The study reported significant heterogeneities between studies ($I^2 = 81.32\%$; $p < 0.0001$).

Diagnosis of diabetes, preoperative hyperglycemia and elevated HbA1c are not likely direct risk factors for PJIs, but more likely to be indirect markers of more serious comorbid conditions (e.g., chronic kidney disease (CKD), peripheral vascular disease (PVD), etc.). Patients, with a sole diagnosis of well-controlled diabetes, do not confer a clinically significant risk for PJIs. However, further evaluation and optimization are necessary for patients with uncontrolled diabetes, end-organ damage or other clinically relevant comorbid conditions. Elevated perioperative glucose and HbA1c are equivocal in predicting PJIs, but should still be optimized in the perioperative period. However, severely uncontrolled diabetes is an absolute contraindication for TJA (e.g., serum glucose ≥ 200 mg/dL). For those with HbA1c ≥ 8 to 9% or glucose levels between 180 to 200 mg/dL, optimization may be a consideration in the preoperative period.

Chronic Kidney Disease (CKD) (Modifiable)

Evidence Strength: Strong

In a retrospective database study by Cavanaugh et al., patients undergoing primary TJA with CKD/end-stage renal disease (ESRD) were associated with a significantly increased risk for SSIs when compared to matched, non-CKD/ESRD controls (OR 1.59; 95% CI 1.14 to 2.21) [57]. When stratified by a patient's dependence on hemodialysis, patients requiring dialysis were at significantly increased risk for SSIs compared to non-dialysis, CKD/ESRD controls (OR 2.44; 95% CI 1.27 to 4.70). When compared to CKD/ESRD patients who underwent renal transplant surgery, dialysis patients also fared significantly worse (OR 2.92; 95% CI 1.93 to 4.42).

The risks of SSIs/PJIs in patients that do not require dialysis is uncertain. In two large separate database studies by Kildow et al. and Erkocak et al., CKD versus non-CKD did not show elevated risks for SSIs or PJIs. However, it should be noted that patient-matching was more extensive in Cavanaugh's study, and that it is difficult to assess the severity of CKD progression in the large database studies.

In a Medicare database study, patients were divided into five cohorts: (1) diabetes mellitus (DM) and THA, (2) DM, THA, CKD, (3) DM, THA, Hemodialysis (HD), (4) DM, THA, Renal Transplant (RT) and (5) age/gender-matched controls. At 90-days, the risk for PJIs increased with worsening comorbidity status: DM/THA OR 2.85 (95% CI 2.54 to 3.19), DM/THA/CKD OR 4.19 (95% CI 3.58 to 4.91) and DM/THA/HD OR 6.61 (95% CI 4.25 to 10.27). DM/THA/RT demonstrated no significant increases in PJI risks over that of control (OR 1.12; 95% CI 0.60 to 2.07), but by 2 years DM/THA/RT became significant with an OR of 1.45 (95% CI 1.04 to 2.04). Compared to previous studies, the risk of PJIs due to diabetes may be synergistic with CKD. This risk is similar to that reported by Cavaughn et al. (OR 2.03, 95% CI 1.53 to 2.7) [57].

In summary, patients with CKD are at increased risks for postoperative SSIs, but require stratification to adequately assess their risk. Current evidence suggests that patients with ESRD requiring hemodialysis fare worse than non-hemodialysis CKD and renal transplant patients. With the reduced risks for postoperative SSIs/PJIs, patients on hemodialysis should be evaluated for renal transplant prior to TJAs.

Clotting Disorders (Non-modifiable)

Evidence Strength: Moderate

Comparative studies examining the effects of clotting disorders and risks for PJIs/SSIs are limited, with most studies reporting only on the natural history or incidence. In a study by Cancienne et al., the risk of PJIs in two cohorts undergoing primary TKAs, hemophiliacs and patients with von Willebrand's disease were compared against those of matched controls without a bleeding disorder [58]. At 3 months, hemophiliacs suffered from a 1.5 greater odds (95% CI 1.2 to 2.0) for PJIs, and patients with von Willebrand's disease trended towards 1.4 greater odds (95% CI 0.9 to 2.1) for PJIs. PJI rates were marked by six

months for both groups (hemophilia OR 1.6 (95% CI 1.4 to 2.0); von Willebrand's disease OR 1.5 (95% CI 1.1 to 2.0)). Large cohort database studies demonstrate inconsistent findings regarding coagulopathies [18,59–61]. However, these studies have failed to sub-analyze the underlying pathologies (e.g., Vitamin K deficiency, von Willebrand's disease, etc.) responsible for abnormal clotting, therefor potentially confounding results.

Currently, the study by Cancienne et al. is the largest, comparative study directly assessing patients with blood clotting disorders. Patients afflicted by clotting disorders are more likely to suffer from PJIs due to their increased risks for hemoarthropathies. Management of these patients, particularly with regards to venous thromboembolism (VTE) prophylaxis, remains challenging. Patients with clotting disorders are relative contraindications to TJA.

Previous Infection of the Operative Joint (Non-modifiable)

Evidence Strength - Strong

In a retrospective cohort study by Pugely et al., patients undergoing elective primary TJAs with a history of previous wound infection were reported to be at a 5.0 greater odds (95% CI 2.3 to 10.9) for SSIs when compared to patients without a history of joint infections [62]. Similarly, in a study of patients afflicted by RA, history of joint infections also resulted in increased risks for postoperative PJIs (OR 5.4; 95% CI 1.87 to 16.14) [63]. Patients reporting previous infections of the joint should be evaluated for active infections with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Surgery should be delayed for those with markers of active infections.

Active Infection (Modifiable)

Evidence Strength - Strong

Systemic or local tissue infections have also been associated with hematogenous or direct seeding of the prostheses after TJA [64–70]. Active infections of an arthritic joint have also been proven to increase the rates of PJIs after TJA substantially [71,72]. A retrospective case-control study found that active *Staphylococcus* septicemia was associated with an increased risk of SSI OR 4.87 (95% CI 1.44 to 15.35) [73]. More interestingly, Radtke et al. reported that preoperative systemic extended-spectrum beta-lactamase bacterial infections within 15 months of THAs significantly increased the risks for PJIs (OR 20.13) [74]. Grammatico-Guillon et al. reported that patients with active ulcers preoperatively had significantly higher rates of SSIs following TJA versus those without ulcers (HR 2.55; 95% CI 1.94 to 3.35) [75]. The authors also showed that patients with urologic inflammatory diseases have also been noted to have increased risks for SSIs after TJAs. However, randomized control trials and metanalyses have indicated that patients with asymptomatic bacteriuria do not appear to be at increased risks for PJIs [76,77]. Moreover, PJI cultures were never the same as the urologic cultures. Larger database studies and retrospective chart reviews have demonstrated no associations between urinary tract infections and PJIs [59,60,78].

In summary, to prevent the catastrophic sequelae of PJIs, active infections of the joint, bloodstream or local tissue are an absolute contraindication to surgery and should be managed prior to performing a TJA.

Human Immunodeficiency Virus (HIV) (Modifiable)

Evidence Strength: Moderate

In a cohort study utilizing the National Inpatient Sample (NIS) database between 1998 and 2010, HIV(+) patients demonstrated a significant 2.78 odds (95% CI: 1.15 to 6.72) of developing SSIs [79]. A similar study by Schairer et al. also reported a 2.06 (95% CI: 1.31 to 3.26) greater odds for PJIs in HIV/Aquired Immune Deficency Syndrome (AIDS) patients, but did not differentiate between the two cohorts. The effects became more evident in the study by Tan et al., which demonstrated 4.44 greater odds (95% CI: 2.47 to 7.99) for PJIs in the AIDS patient population. More recent cohort studies, such as those by Capogna et al. and Lin et al., reported only non-significant trends towards increased infections (OR 6.6 (95% CI 0.64 to 61.0) and OR 3.8 (95% CI 0.06 to 76.75), respectively) in cohorts with HIV [80–82]. Arguably, these discrepancies may be the result of improved HIV antiretroviral therapies and protocols.

Hepatitis co-infection should be investigated and addressed in all patients with HIV. The estimated incidence of hepatitis C co-infection is reported to be 23.2 to 37.0%, and co-infection with hepatitis B is 10.1 to 24.0% [80,83]. In a matched-cohort Medicare database study by Kildow et al., patients were stratified by concomitant hepatitis infections: (1) HIV, (2) hepatitis B virus (HBV), (3) hepatitis C virus (HCV), (4) HIV with HBV or HCV and (5) matched HIV(-) controls [84]. When examining HIV (+) patients only, PJI infections at 90-days post-TKA/THA and 2-years post-THA were not significantly different from HIV(-) controls. Conversely, PJI risks in HIV(+) with HBV(+) or HCV(+) patients were elevated at 90-days post-TKA (OR 2.32; 95% CI 1.27 to 4.25), 2-years post-TKA (OR 2.17 1.48 to 3.18) and 2-years post-THA (OR 2.67 1.59 to 4.47) when compared to matched HIV(-) and HBV(-) and HCV(-) controls.

Similarly, in a meta-analysis of PJIs in HIV only versus HIV with hemophilia patients, hemophilia conferred a 5.28 greater odd (95% CI 2.24 to 11.98) for PJI [85]. A separate analysis was also carried out examining the effects of HIV with and without highly active antiretrovial therapy (HAART) for PJI [85]. Patients receiving HAART were found to have a significantly reduced risk (OR 0.12; 95% CI 0.03 to 0.44) for PJIs [57].

Current recommendations regarding TJAs in patients with HIV indicate all patients undergoing TJA should be initiated on HAART therapy immediately, regardless of CD4+ counts and viral load. Untreated HIV patients are absolutely contraindicated for TJAs. However, due to the logistical nature of clinical studies, no studies to date have been developed to adequately correlate, stratify or control for CD4+ counts and HIV viral loads in relation to PJI outcomes. It is recommended that patients on HAART therapy maintain a preoperative CD4+ count of at least ≥ 200 or greater.

MRSA Colonization (Modifiable)

Evidence Strength: Strong

Outcomes regarding methicillin-resistant *Staphylococcus aureus* (MRSA) colonization in TJA patients have primarily been studied in small sample sizes with highly variable outcomes. Kalmeijer et al. determined that high-level nasal carriage of *S. aureus* was a significant independent risk factor with a risk rate (RR) of 16.0 (95% CI 3.1 to 82.2) for developing an *S. aureus* SSI [86]. Subsequent studies have also demonstrated that THA patients colonized by MRSA have an elevated relative risk for SSIs of 4.46 (CI 95% 1.12 to 17.82; 5.26 vs. 1.17%) when compared to non-colonized cohorts [87]. Similarly, in TKA patients, the RR for SSIs was 5.61 (95% CI 1.81 to 17.38; 7.32 vs. 1.3%). A retrospective analysis of patients with PJI reported *S. aureus* colonization to have a 3.97 greater odds (95% CI 1.49 to 10.54) for PJI compared to control groups [88]. Furthermore, *S. aureus* colonization has been found to have an additive effect with active tobacco use, revision surgery, and/or BMI ≥ 30 kg/m^2, increasing the risk 3 to 12 times that of controls [89]. A number of prospective studies and systematic reviews in both the orthopaedic and general surgery literature

have reported rapid screening and decolonization of *S. aureus* nasal carriers on admission to be effective [90,91].

S. aureus screening and treatment are quick, inexpensive and simple and should be performed on all patients prior to surgery. A small number of patients do not respond to treatment and remain chronic carriers. Although their risk remains elevated for PJIs, continued *S. aureus* colonization is a relative contraindication to elective primary TJA, but may be managed with intraoperative, local vancomycin. However, the use of vancomycin must be balanced against the risk for acute kidney injury [92].

Bacterial Skin Colonization Other Than MRSA (Modifiable)

Evidence Strength: Strong

Preoperative chlorhexidine-based skin preparation has been proposed as a method of reducing SSIs. In a randomized control trial by Kapadia et al., use of chlorhexidine-impregnated clothes the night before or the morning of admission reduced the 1-year PJI rate by 2.5% (2.9 vs. 0.4%) when compared to the previous standard of care (OR 8.15; 95% CI 1.01 to 65.6) [93]. Similar results have been observed in a previous retrospective cohort study (in the same institution) [94,95], as well as in the general surgery patient population [96].

Hepatic Disease

Evidence Strength: Strong

Hepatitis (Modifiable)

A retrospective study by Kuo et al. looking at 3,435 TKA patients in the Taiwanese Longitudinal Health Insurance Database reported that males with HBV had a 4-fold, (OR; 4.32; 95% CI 1.85 to 10.09) increased risk of PJIs compared to those without HBV [97]. The PJI risk was highest 6 months to 1 year following TKA (HR 18.7; 95% CI 1.90 to 184) and decreased after the first year (HR 4.8; 95% CI 1.57 to 14.7). The authors reported no differences in PJI incidences between patients without HBV in the first month. The presence or absence of cirrhosis and HCV infection did not further influence PJI risks in these patients. Interestingly, HBV did not appear to significantly increase the risk of PJIs for females.

In a retrospective, matched control study of 77 HCV(+) TJAs, there were no differences in PJI incidences in HCV(+) versus HCV(-) patients [98]. However, of the two infections in the HCV(+) group, both were deep infections that required reoperation. Meanwhile, both infections in the control group only reported superficial infections that were treated with IV antibiotics. When the HCV cohort was further stratified by disease progression, the incidence of PJIs was noted to be markedly higher in patients whose disease progressed to fibrosis (21 vs. 0%). Kildow et al. reviewed 22,663 TJA patients using the PearlDiver Medicare database and found increased TJA PJI risks for HCV(+) patients at 90-days (OR 1.96; 95% CI 1.53 to 2.50) and 2 years (OR 1.93, 95% CI 1.66 to 2.25), as well as in HBV(+) patients at 2 years (OR 1.66; 1.06 to 2.59) [99]. Although not directly compared to one another, concomitant HIV infection appears to increase infection rates further. With new HCV treatments, it will be important to observe the effects of HCV resolution and PJI outcomes.

Liver Cirrhosis (Modifiable)

To better delineate the effects of cirrhosis versus hepatitis, Jian et al. performed a matched control cohort study using 880,786 TJA patients from the NIS database [82]. When compared to controls, HBV(+) patients without cirrhosis were found to be at no increased risk for PJIs (1.22 (HR; 95% CI 0.77 to 1.95), while HCV(+) patients without cirrhosis were at a 2-fold greater risk for PJI (HR 2.33; 95% CI 1.97 to 2.76), and patients with cirrhosis were at 2.42 greater odds for PJIs (95% CI 1.87 to 3.12). In a large Danish database study by Deleuran et al., deep infection at one year was higher in cirrhotic patients than matched controls (OR 1.65; 95% CI 0.61 to 3.56; 3.1 vs. 1.4%) [100].

Other small, retrospective studies regarding liver cirrhosis demonstrated mixed results. Seol et al. retrospectively compared 71 cirrhotic patients undergoing elective TJA against non-cirrhotic controls [101]. Only a non-significant trend towards increased PJIs (13.5 vs. 5.6%) and SSIs (17.6 vs. 2.8%) was found. It was also noted that most patients who experienced surgical complications were more likely to have chronic comorbidities (e.g., CKD, diabetes and hypertension). Other older studies have described increased rates of wound complications after elective TJAs in patients with asymptomatic liver disease and advanced cirrhosis [102,103]. Similarly, a small study by Cohen et al. has suggested that certain subgroups of cirrhotic patients, specifically Child-Pugh A and B, can safely undergo elective TJA with no increased risk of adverse events [104].

Transplant (Non-modifiable)

Regarding patients receiving a liver transplant, the relative risk of PJIs remains a debated topic, with many studies being only case series. Two case series reported an overall PJI rate of 3.2 to 3.6% [105,106]. A cohort study by Ledford and colleagues reported that organ transplants substantially increased the risks of SSIs or PJIs (3.2%), but there were no differences between groups [106]. One study, which utilized the NIS database, compared the outcomes of 4,493 TJA patients with a history of organ transplantion and revealed that liver transplantion had the greatest increased risks of wound infections and SSIs (OR 3.90, 95% CI: 1.4 to 3.9) compared to kidney, heart, lung and pancreas transplantions [57].

HBV, HCV, cirrhosis and hepatic transplant are relative contraindications to surgery. However, both HCV and cirrhosis present as potentially modifiable risk factors with the advent of HCV immunotherapies and transplant surgeries, respectively. Preliminary evidence points towards HCV treatment prior to TJA. Additionally, the degree of liver cirrhosis and potential risks can be assessed based on the efficacy of serum clotting factors. Due to the lack of conclusive evidence, no strong recommendations can be given at this time for or against HCV immunotherapy, cirrhosis optimization or hepatic transplant prior to TJA. Hepatic panels and coagulation panels should be assessed in patients with end-stage liver disease and surgery should delayed if any bleeding deficiencies are noted.

Chronic Anticoagulation (Non-modifiable)

Evidence Strength: Low

In a matched case-control study by Simpson et al., chronic preoperative warfarin therapy in TKA patients led to: substantially increased hematoma formations within 48 hours (26.8 vs. 7.3%), superficial infections (16.8 vs. 3.3%), deep infections (6.0 vs. 0%) and returns to the operating room (OR) for washout (4.7 vs. 0.7%) [107]. Subset analysis of patients who required heparin-bridging demonstrated markedly higher, deep infection rates when compared to patients who continued warfarin. A similar matched case-control study of THA patients also reported increased rates of deep infections (9 vs. 2.2%) and superficial infections (13.5 vs. 2.2%) [108].

Due to the absence of strong, conclusive evidence or management guidelines, it is recommended for patients on warfarin therapy to be evaluated for other risk factors and optimized appropriately to mitigate the risks of PJI. Bridging of patients on warfarin should be avoided and only performed if absolutely necessary. Future studies

are needed to examine the relationship of International Normalized Ratio (INR), as well as modern-day heparin analogues (e.g., factor Xa inhibitors), with infection.

Alcohol Consumption (Modifiable)

Evidence Strength: Strong

A recent meta-analysis found that alcohol use had a two-fold risk of PJI following TJA (OR 1.88, 95% CI 1.32 to 2.68) [44]. Wu et al. reported similar outcomes in a retrospective study of Chinese patients undergoing TJA (OR2.95; 95% CI, 1.06 to 8.23) [45]. A large, retrospective, matched-control study of 880,786 Statewide Inpatient Database patients illustrated that alcohol use significantly increased the PJI risk after TJA (HR 1.64, 95% CI 1.38 to 1.95) and represented an additive risk factor when present concomitant to cirrhosis [82]. Grammatico-Guillon et al. retrospectively analyzed 32,678 patients in the French Regional Hospital Discharge database and found that alcohol abuse was correlated with a significant increase in SSI risk (HR 2.47, 95% CI 1.67 to 3.63) [75]. The major impact of alcohol abuse on PJI rates was demonstrated by Radtke et al. [74]. After retrospectively reviewing 566 THAs, alcohol abuse was found to increase the odds of PJI by 5.59 (95% CI 95% CI 1.14 to 27.33) within 18 months of surgery. Alcohol consumption has therefore been clearly shown to increase the risk of PJIs for patients undergoing TJAs [18,59–61,109,110]. While there is no defined period of required alcohol cessation prior to TJA, at least four weeks of abstinence has been suggested to reverse physiologic abnormalities associated with excessive alcohol use that predispose patients to increased risk of postoperative morbidity [111].

Alcohol consumption must be assessed on a case-by-case basis. Excessive alcohol consumption is a modifiable risk factor that is a relative contraindication for elective TJA until patients remain abstinent for a minimum of four weeks. However, patients who remain functional in good socioeconomic standing may not require surgical delay.

Smoking (Modifiable)

Evidence Strength: Strong

A recent review reported that 18% of the U.S. population are smokers, placing them at an RR of deep infection after TJA 3.5 times higher than the average population [112]. Tobacco use is growing in the obese population and carries eight times the risk of infection compared to non-obese, non-smokers [88]. In a study by Maoz et al., tobacco use, *S. aureus* colonization and BMI ≥ 30 kg/m^2 were additive in their risks for PJIs (OR 12.76; 95% CI 2.47 to 66.16) [89]. A 2:1 matched-cohort study reported significantly higher surgical complication rates (3.6%) in smokers compared to nonsmokers (0%). Moreover, the majority of revision TJAs performed in the smoking cohort were secondary to infection [113]. In their ACS NSQIP database study, Duchman et al. described a significant increase in the risk of wound complications after TJA in tobacco users (OR 1.47, 95% CI 1.21 to 1.78) [114]. In a comparable large database study, Kremers et al. conveyed similar outcomes with an increased risk of SSI in smokers (HR 1.7, 95% CI 1.1 to 2.6) [115]. Although Singh et al. did not find a significant difference in the rate of SSI in smokers, the authors reported a substantial risk for PJIs when compared to a matched nonsmokers control group (HR 2.28, 95% CI 0.99 to 5.27) [116]. Sahota et al. performed a propensity, score-matched analysis of 12,588 TJA patients in the ACS NSQIP database to assess the effects of smoking on 30-day postoperative complications. The overall 30-day surgical complication rate was higher in current smokers at 2.5% compared to 1.4% in nonsmokers (OR 1.84, 95% CI 1.21 to 2.80). Smokers also exhibited a markedly higher rate of 30-day deep SSIs (1.1%) in a combined THA/TKA cohort. Upon subgroup analysis, active smokers experienced substantially higher incidences of 30-day deep SSIs after THAs (1.3%) and 30-day superficial SSIs following TKAs (1.8%) [117]. A prospective, hospital-registry-based cohort study by Gonzalez et al. found that current smokers had higher one-year postoperative PJI rates than former smokers, both of which were significantly higher than never-smokers (HR 1.8, 95% CI 1.04 to 3.2). Beyond the first year of surgery, the risks of PJIs decreased slightly but remained significantly elevated compared to a history of no smoking (HR 1.12, 95% CI 0.64 to 2.04) [118]. A meta-analysis of six randomized trials demonstrated that smoking cessation had a relative risk reduction of 41% of total postoperative complications. In the same study, the authors pooled data from 15 observational studies and found that patients who discontinued smoking prior to surgery had decreased wound healing complications (RR 0.73, 95% CI 0.61 to 0.87) [119]. On the other hand, Azodi et al. reported that patients partaking in smoking a higher number of packs per year resulted in a significant increased risk of postoperative complications [120]. Moreover, after adjusting the multivariate logistic analysis, the heaviest tobacco smoking group had a 121% increased risk of systemic complications (OR, 2.21; 95% CI 1.28 to 3.82). Smoking represents an independent, modifiable risk factor that significantly compounds the risks of SSIs/PJIs when present alongside other comorbidities. Therefore, active smoking, especially heavy tobacco use, represents a relative contraindication to TJA until enrolled in a smoking cessation program for at least four weeks.

Intravenous Drug Abuse (Modifiable)

Intravenous drug abusers (IVDA) can often present with HIV, creating a myriad of risks that are problematic to treat. Previous retrospective studies have described a four-fold increase in septic arthritis of native joints in IVDA versus non-IVDA patients [121,122]. A retrospective study by Lehman et al. reported higher rates of PJIs in IVDA and/or HIV(+) patients [123]. IVDA also carried almost twice as high PJI incidences (25%) compared to HIV(+) only patients(14%). When IVDA and HIV were both present, the rates of PJIs increased to 40%. More recent studies confirmed that IVDA was a significant risk factor for THAs and resulted in higher odds of PJIs in orthopaedic surgery [109,124]. The risks of PJIs continue well past the primary TJA, and substantially impacts ensuing revision procedures. Su et al. reported an estimated 25% survival, free of reinfection rates, for two years in IVDA patients compared to 96% in control revision THA patients [125]. Pitta et al. conducted a prospective cohort study of 405 failed primary TKAs [126]. Their study demonstrated that IVDA was a significant risk factor for TKA failure and correlated with a five-fold increase in risk for revision surgery. Two retrospective reviews of IVDA within 1 year of THA and TKA described failure rates as high as 50%, complicated revision procedures and a 17% amputation rate [127,128]. The unacceptable PJI rates, leading to complex salvage procedures and high failure rates after primary and revision surgeries, make TJA in active IVDAs futile and an absolute contraindication. Patients should be referred to appropriate drug counseling programs and be offered surgery only after remaining abstinent from drug use for a minimum of one year.

Osteonecrosis (Non-modifiable)

Evidence Strength: Moderate

Evidence regarding osteonecrosis and its relation to SSIs/PJIs is highly conflicting. Currently, the three identified studies in this systematic review were all derived from the Kaiser Permanente Total Joint Replacement Registry (TJRR). In two studies by Namba et al.,

similar methods were applied to evaluate the effects of osteonecrosis on SSIs/PJIs; one focused on THAs while the other focused on TKAs [42,129]. Both studies demonstrated an increased risk for SSIs/PJIs in TJA candidates with osteonecrosis. However, a third study by Singh et al. [130], which contained many overlapping authors from the Namba et al. studies and utilized the TJRR, extended the original 8-year database to 11 years, and found no increases in SSIs/PJIs in THA candidates with osteonecrosis. Due to the conflicting evidence and high potential for study bias, osteonecrosis of the hip is not a strong risk factor for SSIs/PJIs in TJA candidates.

Age (Non-modifiable)

Evidence Strength: Moderate

There is inconsistent evidence on whether age contributes to increased risks of PJIs. The meta-analysis by Chen and colleagues showed no associations between age and risk of infection [46]. In a pooled analysis of eight studies, age (as a continuous exposure) was not associated with the risks of PJI [19]. However, findings from two studies suggested that patients 75 years old and above had an increased risk of SSIs following primary THAs [131,132].

Gender (Non-modifiable)

Evidence Strength: Moderate

The effects of gender on the risks of PJIs have been mostly inconsistent. While some studies suggest males are at an increased risk of developing PJIs following joint arthroplasty, others suggest the contrary. In a pooled analysis of eight studies, Chen et al. demonstrated that males had a higher risk of infection after TKA than females [46]. Recent pooled multivariate analysis of 28 studies confirms the emerging evidence [19].

Race (Non-modifiable)

Evidence Strength: Strong

Pooled analysis shows that black and Hispanic populations have increased risks of developing PJIs/SSIs, when compared to white populations [42,61,133].

Location (Non-modifiable)

Evidence Strength: Limited

One study reported an increased risk of infections for patients residing in rural locations as opposed to urban locations in China [45]. However, this may be the result of a country's care system as opposed to geographic location.

Hip vs. Knee Arthroplasty (Non-modifiable)

Evidence Strength: Strong

Compared to THAs, TKAs were consistently associated with increased risk of PJIs/SSIs [73,134].

Underweight (Modifiable)

Evidence Strength: Strong

Three studies compared underweight (BMI < 18.5 kg/m^2) vs. normal vs. overweight BMI categories and found no associations with PJIs [13,14,129].

Hypertension (Modifiable)

Evidence Strength: Strong

Pooled analysis of four large database studies with matched controls showed no significant evidence of associations between hypertension and the risks of PJIs/SSIs [18,59,60,135].

Socioeconomic Status (Non-modifiable)

Evidence Strength: Strong

Consistent evidence showed that a low income was associated with increased risks of PJIs/SSIs [136–138].

Electrolytes (Modifiable)

Evidence Strength: Strong

There was no significant evidence of associations between electrolyte imbalances and risks of PJIs/SSIs [18,62].

Depression (Modifiable)

Evidence Strength: Strong

Evidence suggested histories of depression and psychosis to be associated with increased risks of PJIs following TJA [18,59,60].

Steroids (Modifiable)

Evidence Strength: Moderate

A previous meta-analysis of four studies suggested a history of steroid therapy to be associated with increased risks of PJIs following TKAs [46]. In a pooled analysis of five studies, Zhu et al. also demonstrated steroid therapy to be associated with increased risks of PJIs following TJA [48]. In the most recent pooled analysis of 10 studies, the findings were consistent with previous evidence [19].

Cardiovascular Disease (CVD) (Modifiable)

Evidence Strength: Strong

A pooled analysis of seven studies reporting inconsistent findings showed a history of CVD to be associated with increased risks of PJIs/SSIs following TJAs [59,60,78,139–143]. In a pooled analysis of studies that evaluated congestive heart failure (CHF) and cardiac arrhythmias as risk factors, significant associations were demonstrated [5,18,59,60,133].

Peripheral Vascular Disease (PVD) (Modifiable)

Evidence Strength: Strong

A pooled analysis of six studies should a history of PVD is associated with increased risks of PJIs/SSIs [5,18,59,60,82,144].

Lung Disease (Modifiable)

Evidence Strength: Strong

The presence of chronic pulmonary diseases remains equivocal. While pooled analysis of four studies evaluating the associations of chronic pulmonary disease with risk of PJIs showed no evidence of an association [5,59–61], two studies reported consistent associa-

tions. With regards to chronic obstructive pulmonary disease, specifically, an increased risk for PJIs/SSIs was noted in a pooled analysis of four studies [3,73,133,135].

Rheumatoid Arthritis (RA) (Modifiable)

Evidence Strength: Moderate

A pooled analysis of seven studies showed RA to be associated with increased risks of PJIs following TKAs [46]. In another pooled analysis of seven studies, Zhu et al. demonstrated RA to be associated with increased risks of PJI [48]. Findings of a recent pooled analysis of 13 studies confirms the accumulating evidence [19] .

Malignancy (Non-modifiable)

Evidence Strength: Strong

A history of cancer or malignancy was associated with increased risks of PJIs/SSIs following arthroplasty in a pooled analysis of seven studies [18,59–61,73,145,146]. However, evidence on the associations between metastatic tumors and risks of PJIs/SSIs was limited and inconsistent [5,18,59,60].

Previous Joint Surgery (Non-modifiable)

In a pooled analysis of five studies, a history of previous joint surgery (vs. no previous joint surgery) was associated with a threefold increased risk of PJIs [19]. When compared to primary arthroplasties, revision arthroplasties were associated with increased risks of PJIs in a pooled analysis of five studies [19]. Two studies reported a history of previous joint infections to be associated with increased risks of PJIs, but these findings were based on univariate analysis [3,63].

Frailty (Modifiable)

Evidence Strength: Moderate

A single, high-quality study reported increased risks of PJIs comparing frail patients with non-frail patients [147].

Anemia (Modifiable)

Evidence Strength: Strong

Consistent evidence showed that preoperative anemia was associated with increased risks of PJIs/SSIs following TJAs [5,59,60,148].

ASA (Non-modifiable)

Evidence Strength: Strong

An ASA grade of > 2 was associated with increased risks of PJIs/SSIs; this was consistent across all studies [42,89,129,131,133,134].

Charlson Comorbidity Index (Modifiable)

Evidence Strength: Strong

Though the exposures were not comparable, and therefore could not be pooled, there was consistent evidence showing a higher Charlson Comorbidity Index to be associated with an increased risk of PJIs/SSIs [136,137,149].

Osteoarthritis (Non-modifiable)

Evidence Strength: Strong

Pooled evidence from seven studies showed no significant associations of osteoarthritis with the risks of PJIs following joint arthroplasties [42,109,129,130,150,151].

Post-Traumatic Arthritis (Non-modifiable)

Evidence Strength: Strong

Pooled analysis of three studies showed no evidence of associations between post-traumatic arthritis and risks of PJIs/SSIs [42,129,152].

Dental Procedures (Non-modifiable)

Evidence Strength: Limited

In two studies that evaluated the associations of dental procedures with risks of PJIs, there was no evidence of any significant associations [45,145].

Neurologic (Modifiable)

Evidence Strength: Strong

A history of neurologic disease such as hemiplegia/paraplegia was associated with increased risks of PJIs/SSIs in a pooled analysis of four studies with inconsistence findings [59–61]. The results were the same for dementia and PJIs/SSIs [59,60,73].

Hypercholesterolemia (Modifiable)

Evidence Strength: Strong

None of the studies, which evaluated the associations of hypercholesterolemia and peptic ulcer disease with the risks of PJIs, showed any evidence of associations [18,59,60].

Valvular Disease (Non-modifiable)

Evidence Strength: Strong

Evidence regarding the associations between valvular diseases and risks of PJIs/SSIs was limited and inconsistent [18,59–61]. In the pooled analysis, there was no significant evidence of PJIs/SSIs being associated with a history of pulmonary circulatory disorders [5,59–61], a history of hypothyroidism [18,59,60,153], or a history of drug abuse [18,59,60].

Transfusion (Non-modifiable)

Evidence Strength: Strong

Patients who receive allogenic blood transfusions are at increased risks of SSIs/PJIs [5,134,154–156]; however, the evidence is limited for autogenic blood transfusions [5]. Prophylaxis with warfarin or low molecular weight heparin for venous thromboembolism was associated with increased risks of PJIs [157,158].

Methods and Materials: Manuscripts pertaining to host-related risk factors for PJIs were searched using PubMed, ScienceDirect, and Web of Science, with a date restriction of January 1, 2013 to February 23, 2018. The following search queries and their results are listed in the following chart:

Database	Search Term/Filter	Results
PubMed	("arthroplasty, replacement, hip"[MeSH Major Topic] OR "arthroplasty, replacement, knee"[MeSH Major Topic]) OR ("knee"[TITLE] OR "hip"[TITLE]) AND ("arthroplasty"[TITLE] OR "replacement"[TITLE]) AND ("infection"[MeSH Major Topic] OR "deep infection"[TITLE] OR "PJI"[TITLE] OR "Prosthetic Joint Infection"[TITLE] OR "Periprosthetic Joint Infection"[TITLE] OR "Surgical Site Infection"[TITLE] OR "SSI"[TITLE]) NOT ("autobiography"[Publication Type] OR "comment"[Publication Type] OR "congresses"[Publication Type] OR "dictionary"[Publication Type] OR "editorial"[Publication Type] OR "interview"[Publication Type] OR "lectures"[Publication Type] OR "legal cases"[Publication Type] OR "legislation"[Publication Type] OR "letter"[Publication Type] OR "news"[Publication Type] OR "newspaper article"[Publication Type] OR "patient education handout"[Publication Type] OR "periodical index"[Publication Type] OR "personal narratives"[Publication Type] OR "technical report"[Publication Type] OR "webcasts"[Publication Type]) AND "last 5 years"[PDat] AND English[lang]	510
ScienceDirect	pub-date > 2012 and TITLE-ABSTR-KEY(((("hip arthroplasty" OR "hip replacement") OR ("knee arthroplasty" OR "knee replacement")) AND infection)	956
Web of Science	((TI=(("hip arthroplasty" OR "hip replacement" OR "knee replacement" OR "knee arthroplasty") AND (infection OR PJI OR SSI)))) AND LANGUAGE:(English) AND DOCUMENT TYPES: (Article OR Abstract of Published Item OR Data Paper OR Database Review OR Early Access OR Review)	246
	Total	1712

These results were subsequently imported into Mendeley Reference Management Software (Elsevier, Amsterdam, Netherlands) and 347 duplicates were removed. These abstracts were then imported into the Rayyan (Qatar Computing Research Institute, Doha, Qatar) for subsequent screening of titles and abstracts by authors J.E.F. and Z.C. Of the 1,365 abstracts collected, 1,126 were excluded due to incorrect study topic, foreign language, or low study quality (case reports and case series without comparative groups). Of the remaining abstracts, 239 remained for full-text article review with study quality assessment using the American Academy of Orthropaedic Surgeons (AAOS) Clinical Practice Guideline and Systematic Review Methodology guidelines [159]. The Relative Risk, Odds Ratios, and Hazard Ratios, as well as incidences and statistical significances, were used to assess outcomes of prosthetic joint-related infections.

A separate systematic review was performed by S.K. Data sources included Medline, Embase, Web of Science, Cochrane Library and reference lists of relevant studies from inception to February 15, 2018. Studies of interest were longitudinal studies (observational studies and randomized controlled trials (RCTs)) that have evaluated the associations of patient-related factors and the risk of SSIs and/or PJIs in patients undergoing orthopaedic procedures. Of 7,177 potentially relevant citations, 69 studies were finally included in this review. No RCTs relevant to the review topic were identified.

What modifiable and non-modifiable host factors contribute to an increased risk of SSI/PJI?

Modifiable host risk factors for PJI/SSI in TJA:

- Active Infection
- Alcoholism
- Cardiovascular Disease
  - Congestive Heart Failure
  - Cardiac Arrhythmia
- Chronic Kidney Disease
- Chronic Obstructive Pulmonary Disease
- Clotting Disorders
- Depression
- Diabetes Mellitus
  - HbA1c
  - Serum Glucose
- Drug Abuse
- End-stage Renal Disease
- Frailty
- HIV/AIDS
- Immunosuppression
- Intra-articular Steroid/Viscosupplement Injection
- Kidney Disease
- Malnutrition
- MRSA Colonization
- Obesity
- Peripheral Vascular Disease
- Psychosis
- Renal Disease
- Rheumatoid Arthritis
- Skin Colonization
  - MRSA/MSSA
- Smoking
- Untreated HCV

Non-modifiable host risk factors for PJI/SSI in TJA:

- Age
- ASA >2
- Bariatric Surgery
- Chronic Anticoagulation
- Gender
- Hemiplegia/Paraplegia
- HBV
- Osteonecrosis
- Previous Joint Surgery
- Previous Joint Infection
- Previous Infection
- Transplant

In addition to identifying pertinent risk factors for PJIs, what is the acceptable total risk for patients undergoing elective, primary

TABLE 1. Definitions

	Modifiable Risk Factor	Non-modifiable Risk Factor
Absolute Contraindication	**Absolute modifiable risk factor**: A risk factor that is associated with a preventable complication and delays surgery until it is appropriately evaluated and optimized.	**Absolute non-modifiable risk factor:** A risk factor that cannot be optimized and precludes the patient from receiving surgery. Alternative therapies for joint pain should be pursued.
Relative Contraindication	**Relative modifiable risk factor:** A risk factor that is modifiable but does not require surgical delay if no other risk factors are present. However, when the patient's risk for postoperative complications crosses the threshold of acceptability, this risk should be optimized.	**Relative non-modifiable risk factor:** A risk factor that is non-modifiable and does not require surgical delay. For patients with additional risk factors which cross the threshold of acceptability, other modifiable risk factors should be optimized prior to surgery.

TJAs? The Readmission Risk Assessment Tool (RRAT) was specifically developed to reduce the incidence of preventable hospital readmissions in patients undergoing elective TJA [160]. The RRAT includes eight distinct risk factors and uses a weighted score to quantify a patient's risk of readmission (e.g., MRSA colonization – 3 points, Smoking – 1 point, BMI ≥ 40 – 3 points, etc.). With nearly 45% of readmissions being due to SSIs, the RRAT is a powerful tool to identify and optimize patients at risk for PJIs. Despite the development of these powerful tools, a discussion regarding an ethically and financially acceptable risk cutoff for PJI is still required.

When does the accumulated relative risk of infection due to comorbidity burden (modifiable, non-modifiable or a combination) become unacceptable to proceed with TJA?

Examples:

- **Modifiable risk factors that are absolute contraindications (Absolute MRF):** Untreated HIV, serum glucose ≥ 200, active sepsis, active joint infection, intra-articular injections within three months, active intravenous drug use, super obesity (BMI ≥ 50 kg/m^2)
- **Modifiable risk factors that are relative contraindications (Relative MRF):** Obesity, elevated HbA1c, smoking, catastrophizers, high fall-risk patients, non-metastatic cancer, malnutrition, hepatitis C
- **Non-Modifiable risk factors that are absolute contraindications (Absolute Non-MRF):** Pulmonary hypertension
- **Non-modifiable risk factors that are relative contraindications (Relative Non-MRF):** Gender, age, hemiparesis, metastatic cancer, blood clotting disorders, hemophilia, von Willebrand's, previous infection of the operative joint, liver transplant, kidney transplant, hepatitis B

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QUESTION 2: Is the diagnosis of post-traumatic arthritis associated with increased risks of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) after joint arthroplasty?

RECOMMENDATION: Yes. Total joint arthroplasty (TJA) for patients with post-traumatic arthritis of the hip or knee carries higher risks of developing SSIs/PJIs. The incidence is markedly higher in patients with previous surgeries and retained implants.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Symptomatic arthritis of the hip, knee and ankle has been reported to be secondary to traumatic causes 12% of the time [1]. There have been few high-quality studies assessing the impacts of the preoperative diagnoses on the risks for SSIs and PJIs. However, numerous

studies have evaluated clinical and radiographic outcomes following TJAs for post-traumatic arthritis, but often lack a comparison group [1–14]. Moreover, studies have shown total knee arthroplasty (TKA) with retained hardware from a tibial plateau fracture is associated with a higher incidence of PJI compared to TKA for patients without retained hardware [15].

Bala et al. evaluated surgical complications among 3,509 patients undergoing TKA for post-traumatic arthritis in comparison to 257,611 controls from the Medicare database with at least two years of follow-up [1]. They found that post-traumatic arthritis patients were at a 4.93% risk of deep infection, compared to a 2.93% risk among the primary osteoarthritis group, for a significant odds ratio of 1.72 (95% confidence interval (CI) 1.47 to 2.01). Pedersen et al. used the National Danish Registry to evaluate risk for revision due to infection among 9,380 patients undergoing total hip arthroplasty (THA) due to arthritis following proximal femoral fractures compared to 63,318 control patients undergoing THA for primary osteoarthritis [16]. Post-traumatic THA patients experienced a 0.94% rate of deep infections, compared with 0.70% for primary osteoarthritis patients, for a non-significant difference in adjusted relative risk of 1.46 (95% CI 0.99 to 2.17). Similar results were observed in the Danish Knee Arthroplasty Registry that noted revisions were more frequent in post-traumatic arthritis knee patients [17]. Database studies have also been used to identify risk factors for SSIs/PJIs, which have shown higher infection rates in patients diagnosed with post-traumatic arthritis [18,19].

Saleh et al. performed a systematic review of TKAs for the treatment of post-traumatic arthritis that included 16 prospective and retrospective studies [10]. Primary outcomes focused on clinical function scores. Rates among the population that reported infection as a complication totaled 20.9% for superficial infections (62/296 total patients) and 16.5% for deep infections (67/405 total patients). No comparison groups were available for analysis among these studies. These proportions are higher than most published rates of PJIs for TKAs performed due to primary osteoarthritis. Similarly, a systemic review assessed the outcomes of THAs following acetabular fracture and noted that the risk of infections in THAs following acetabular fractures was higher than that for conventional hip arthroplasties, especially in patients with multiple prior surgeries and retained hardware from previous acetabular reconstruction [20].

Other studies provided proportions of PJIs as a secondary outcome among post-traumatic patients and primary osteoarthritis patients. Ge et al. performed a retrospective review of 27 patients who underwent TKAs following periarticular fracture compared to 45 patients who had a history of soft tissue injury about the knee without fracture [3]. Small numbers of PJIs were reported with two reported superficial infections in each group (7.4% vs. 2.3%) and four deep infections in the fracture group (15%) compared to zero in the soft tissue group. Lunebourg et al. reported on functional outcomes following TKAs. They compared 33 patients with a history of periarticular fractures with 407 primary osteoarthritis controls [6]. No superficial infections were reported in the post-traumatic group compared to one in the primary osteoarthritis group (0.02%), while two deep infections were reported in the post-traumatic group (6.1%) compared to zero in the primary osteoarthritis group. Scott et al. evaluated clinical outcomes of TKAs following tibial plateau fractures among 31 patients compared to a matched cohort of 93 primary osteoarthritis patients [12]. They reported four superficial infections in the post-traumatic group (12.8%) compared to one in the primary osteoarthritis group (1%). They reported one deep infection in each group (3.2% vs. 1%). Morison et al. performed a retrospective case-control study of patients who underwent THAs after acetabular fracture vs. a matched cohort of patients who had received THAs for primary osteoarthritis or avascular necrosis [21]. The authors observed that patients with a previous acetabular fracture had a higher likelihood of developing infections.

Further studies only reported infection rates for the post-traumatic patients without a comparison group. Proportion of patients experiencing infection in these studies ranged from 3.2 to 26.7% for superficial, and 3.2 to 20% for deep [2,4,5,7–9,11,13,14,22]. Only one study evaluated the risks of PJIs following THAs. All other included studies focused on PJIs following TKAs as a primary or secondary outcome. We conclude that a rate of PJIs following TJA for post-traumatic arthritis is likely higher than TJAs for primary osteoarthritis. However, few studies are evaluating this topic as a primary outcome, and the majority of these have limited number of infection events available for analysis.

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QUESTION 3: What nutritional markers are the most sensitive and specific for surgical site infections and periprosthetic infections (SSIs/PJIs)? Does improvement in nutritional status reduce the risk of SSI/PJI?

RECOMMENDATION: Serum albumin < 3.5 g/dL has been demonstrated to be an independent risk factor for SSIs/PJIs following total joint arthroplasty in multiple, large-scale studies. However, other nutritional markers are poorly studied. Currently, there is insufficient evidence to prove that correction of preoperative nutritional markers reduces the risks of subsequent SSIs/PJIs. Despite the absence of such evidence, we recognize the importance of an optimized nutritional status before total joint arthroplasty (TJA) to reduce the risks of SSIs/PJIs.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

It is well established that malnutrition is associated with an increased risk of a number of adverse outcomes following TJA, including wound healing problems, longer hospital stays and PJIs [1–3]. The prevalence of malnutrition in patients undergoing orthopaedic procedures has been reported to be as high as 50% [4]. However, it is unclear which nutritional markers are most sensitive and specific for SSIs and PJIs. Serologic values and anthropometric measures have been utilized to determine nutritional status.

Serologic markers commonly used as markers of malnutrition include serum albumin concentration < 3.5 g/dL, serum total lymphocyte count (TLC) of <1500 cells/m^3 and serum transferrin < 200 mg/dL. Other serum markers, including serum prealbumin, have been discussed in nutritional literature but levels for malnutrition have been poorly defined in the orthopaedic literature.

Gherini et al. evaluated preoperative serum albumin and transferrin levels in patients undergoing primary total hip arthroplasty (THA) and found that delayed wound healing was associated with a lower preoperative serum transferrin (226 mg/dl in complicated cases vs. 262 mg/dl in those that did not have any complications) [5]. Alfargieny et al. found that serum albumin, but not serum TLC, was an independent predictor of SSIs following primary THA [6]. Other recent studies have also identified serum albumin as an independent predictor of SSIs and PJIs [2,6–12]. Studies of 37,173 patients undergoing total knee arthroplasty (TKA) and 49,475 patients undergoing THA in the American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) database found that albumin < 3.5 g/dL was a stronger independent predictor of SSI and mortality than obesity [8,13]. The superficial SSI rate was 2.14% in patients with hypoalbuminemia vs. 0.71% in patients with normal serum albumin following THA and 1.27 vs. 0.64% following TKA. The deep SSI rate was 0.38% in patient with serum albumin ≥ 3.5 g/dL vs. 0.12% in patients with hypoalbuminemia following TKA and 0.71 vs. 0.27% in THA [8,13].

In the revision TJA setting, low serum albumin has also been found to be an independent risk factor for postoperative SSIs and PJIs. Yi et al. evaluated the associations between malnutrition, septic failure and acute infection occurring after revision TJAs. The nutritional parameters used were serum albumin, TLC and transferrin. They found that in the presence of one or more altered parameters, suggestive of malnutrition, that these independently associated with both chronic PJIs and acute postoperative infections [2]. Bohl et al. found that patients undergoing revision TJA with hypoalbuminemia were more than twice as likely to develop PJIs within 30 days than those with serum albumin > 3.5 g/Dl [11].

Anthropometric measures such as calf circumference, arm muscle circumference and triceps skinfold have been utilized to identify undernutrition in orthopaedic patients, but cutoffs are poorly defined and correlations with SSIs and PJIs are not well studied [14–17].

Serum albumin is the most widely studied nutritional marker in patients undergoing TJA. Due to the correlations between nutritional status and postoperative complications, patients suspected of malnurishment should have nutritional parameters evaluated prior to elective arthroplasty. However, there is currently inadequate evidence to determine whether correction of preoperative nutritional markers results in decreased rates of SSIs and PJIs.

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1.2. PREVENTION: RISK MITIGATION

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QUESTION 1: What preoperative screening for infections should be performed in patients undergoing revision hip or knee arthroplasty because of presumed aseptic failure?

RECOMMENDATION: In addition to taking a thorough history, obtaining radiographic imaging and performing a physical examination, all patients with a failed hip or knee arthroplasty awaiting revision surgery should have their serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) measured. Patients with high index of suspicion for infection should be considered for further workup.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 96%, Disagree: 4%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

While there are many etiologies that can cause pain and failure following total joint arthroplasty (TJA), infection is the most common cause of failure in total knee arthroplasty (TKA) and the third most common cause of failure in total hip arthroplasty (THA) [1,2]. The evaluation of patients with a painful TJA begins with a thorough history, physical examination and joint-specific radiographic imaging.

Patients with recent bacteremia, prolonged drainage after surgery, multiple surgeries on the same joint, history of prior periprosthetic joint infections (PJIs), history of surgical site infections of the same joint, comorbidities resulting in an immunocompromised state (i.e., diabetes mellitus, inflammatory arthropathy, etc.) or patients with increased risks of skin barrier penetrations (i.e., intravenous drug abuse, skin ulceration, chronic venous stasis, etc.) should be considered at higher risk for PJIs [3]. Physical exam findings suggestive of PJIs include joint erythema, warmth or large atraumatic effusion.

Plain radiographs should be obtained for all patients presenting with a painful TJA. It is useful to compare serial radiographs. Plain radiographic findings that should increase suspicions of PJIs include signs of early loosening, early osteolysis, periosteal elevation and transcortical sinus tract [4,5]. However, it is important to note that radiographs are rarely diagnostic of PJIs, and can often be normal in the setting of infection.

Infection can be an occult cause of pain following TJA. Therefore, screening for PJIs should be performed in every patient with a painful hip or knee arthroplasty. A successful screening test should have high sensitivity, be widely available and cost-effective. Serum inflammatory markers have been a cornerstone for screening for PJIs in the painful TJA [3–9]. Obtaining an ESR and CRP have proven to be effective screening tools for PJIs due to their high sensitivity, wide availability and cost-effectiveness [10–18]. Using ESR and CRP in combination improves sensitivity and negative predictive values [10,13,14,17–20].

It is important to note that ESR and CRP levels below established thresholds do not definitively exclude the possibility of PJIs [10,13,20]. This is especially true of patients with slow growing organisms such as *Cutibacterium acnes* (*C. acnes*) [21]. It is also true that patients with elevated serological markers do not definitely have PJIs. It is recommended that in the presence of elevated serology and/or high, clinical suspicion for PJIs, even in the presence of normal serology, joint aspiration be performed [3,5,7].

There are some additional limitations to screening using inflammatory markers. ESR, especially, and CRP are normally elevated in the early postoperative periods. Patients with elevated metal ion levels can also present with elevated ESR and CRP levels creating a clouded diagnostic picture [9]. In an effort to overcome these shortcomings, other serum biomarkers have been studied for the diagnosis of PJIs. Interleukin-6 (IL-6) is a cytokine produced by activated monocytes, macrophages and T-cells and has been shown to be a highly-sensitive and specific biomarker for PJIs. However, selection bias, cofounding variables and small study sizes have limited its wide spread adoption [11,22–24]. In a recent study, Shahi et al. evaluated serum D-dimer (fibrinolytic by-product) as a marker of PJIs. In their study, D-Dimer outperformed both ESR and CRP individually and when combined in terms of sensitivity and specificity for diagnosis of PJIs [20]. While promising, this was the first study to analyze the role of D-dimer in diagnosing PJIs.

It is clear that there is a need for more specific and accurate serological screening tests in order to diagnose PJIs. The future holds

promise as the role of new serological markers are being evaluated. Until a more accurate serum marker is introduced, we recommend that any patient with suspected diagnosis of PJI be screened using serological tests for inflammation, namely, CRP and ESR. Consideration should also be given to testing D-dimer as a potential supplementary serological test.

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QUESTION 2: Does prior septic arthritis (aerobic, anaerobic, fungal, tuberculosis) of a native joint predispose the patients to an increased risk of subsequent periprosthetic joint infection (PJI) in the same joint receiving arthroplasty? If yes, how soon after a prior septic arthritis can elective arthroplasty be performed in the same joint?

RECOMMENDATION: Yes. A prior septic arthritis in a joint does predispose the same joint to subsequent PJI after arthroplasty. In the absence of concrete evidence, we recommend that arthroplasty be delayed at least until completion of antibiotic treatment and resolution of clinical signs of infection, but no earlier than three months from the inciting event.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 87%, Disagree: 9%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

The role of total joint arthroplasty (TJA) in patients with prior septic arthritis is not clearly defined. The number of variables involved in such cases have made all current, cohort-based studies difficult to statistically compare. These variables include, age of onset of septic arthritis (child vs. adult), septic joint with or without osteomyelitis involvement, type of joint infected (knee vs. hip), operation performed (one-stage vs. two-stage), time between septic joint and TJA or time between stages for two-stage procedures, and the initial organism causing septic arthritis (tuberculosis vs. bacterial). These variables, among others, are important because they contribute to substantial heterogeneity between patients being treated under the blanket term of having prior septic arthritis.

Previous studies have often grouped patients with differing amounts of these variables together and have reported low-powered and inconclusive results. We performed a systematic review of the literature [1–51] including studies that have directly compared this patient population to those undergoing primary TJA at the same institution by the same surgeons to assess whether or not patients

with prior septic arthritis are at an increased risk of PJIs [39]. A case-control study of 36 total patients (18 in each cohort) found no significant differences in the infection rates between patients undergoing TJA for osteoarthritis and those who had prior septic arthritis [39]. This study was limited by its small size and, as the authors suggest, larger studies are needed to make an accurate statement about the comparative PJI rates.

In the largest published series to-date, Kim et al. reviewed 170 patients (85% infected with *Staphylococcus aureus*) undergoing one-stage total hip arthroplasty (THA) with quiescent infection (mean 33 years post-infection), all of which had septic arthritis in childhood [30]. In this series, all patients, except for one (two hips), had THA at least 10 years after septic arthritis and the only hips that were complicated by PJIs after THA were those two hips that had a quiescent period of seven years. The authors recommended that a 10-year quiescent period be the minimum required to undergo THA after septic arthritis [30]. In contrast, another large cohort by Seo et al. reported on 62 patients (42% methicillin-resistant *Staphylococcus* species) undergoing one-stage total knee arthroplasty (TKA) after a mean quiescent period of only 4 years, all of which had adult-onset septic arthritis with a PJI rates of 9.7% [43]. Jerry et al. evaluated 65 patients (20 with osteomyelitis and 45 with septic arthritis) undergoing one-stage TKA with an average quiescent period in both groups of 18 years [25]. The series reported PJI rates of 15% in the osteomyelitis cohort and 4% in the septic arthritis group [25]. All of these studies demonstrate the heterogeneity of the current literature on this topic.

In patients undergoing THA for tubercular arthritis, the recommended periods of quiescence before THA varies from immediate to 10 years [29,38,46]. However, reactivation has been reported even in cases operated on after a quiescent period of 37 to 40 years [50]. Hence, as a part of preoperative assessment, only patients who had completed a full course of antitubercular treatment (ATT) therapy were considered for THA. A recent systematic review of THA in tuberculosis of the hip by Tiwari et al. [51] concluded that ATT be given for at least two weeks preoperatively and continued for 6 to 18 months postoperatively to minimize reactivation rates. The study also indicated that patients with draining sinuses should be disqualified from undergoing one-stage THA and should instead undergo a two-stage procedure [51].

Because of the limitations of the current literature, the statistical analyses performed on these studies at this time has been restricted to pooled, weighted infection rates inclusive of 1,300 TJAs (Table 1). In order to address the heterogeneity problem, we have subdivided the cohort into subgroups including one-stage and two-stage procedures, adult onset septic arthritis and childhood (< 18 years) onset septic arthritis, etc. This data demonstrates a PJI rate of 8.26% for TKAs and a 5.20% rate for THAs, while both bacterial septic joint and tuberculous septic joint achieved PJI rates around 6%. Next, we subdivided the cohort by the treatment type (one-stage vs. two-stage procedures) and then performed the analyses by further dividing each of these two groups (Table 2). Weighting and pooling the data this way allowed for more homogenous analyses, but further divisions within each of these cohorts were not possible due to sample size limitations. As mentioned, comparative statistics were not possible on these infection rates due to limitations in individual study designs.

To conclude, patients with prior septic arthritis undergoing TJA in the same joint have an increased rate of infection compared to patients undergoing primary TJA without prior septic arthritis. The following recommendation is based on the limited data currently available: management of septic arthritis by arthroplasty using the following protocol (two-stage TJA in the case of active/evolving arthritis and one-stage TJA in the case of quiescent arthritis) may yield good functional results. This is the only study to date directly comparing the one- and two-stage TJAs demonstrating infection control rates of up to 87% in active/evolving septic arthritis and up to 95% in quiescent arthritis [11]. The literature still lacks appropriately-sized, randomized clinical trials or prospective, comparative case-control studies to better support these recommendations.

TABLE 1. PJI rates for TJA following prior septic arthritis of same joint

Pooled Cohort Type (n)	PJI Rate (Same Joint)	95% CI
All studies, pooled (n=1300)	5.96%	4.24 to 7.94
One-Stage TJA, pooled (n=1020)	5.14%	3.31 to 7.36
Two-Stage TJA, pooled (n=280)	8.70%	5.77 to 12.49
Bacterial Septic Joint, pooled (n=977)	5.84%	3.97 to 8.05
TB/mycoplasma Septic joint, pooled (n=323)	6.09%	2.94 to 10.28
Adult-onset Septic Joint, pooled (n=717)	8.35%	6.48 to 10.55
Childhood-onset Septic Joint, pooled (n=583)	2.18%	1.16 to 3.70
Hip Septic Joint to THA, pooled (n=1037)	5.20%	3.50 to 7.21
Knee Septic Joint to TKA, pooled (n=263)	8.26%	5.30 to 12.15
Total Primary TJA (from literature) [1-6]	0.4%-1.5%	NA

PJI, periprosthetic joint infection; TJA, total joint arthroplasty; CI, confidence interval; TB, tuberculosis; THA, total hip arthroplasty; NA, not available

TABLE 2. Infection rates by stage, subdivided by groups to decrease heterogeneity

	All Septic Arthritis to TJA (n=1300)							
	One-stage Procedure				Two-stage Procedure			
Age at SA	Adult Onset (n = 437)	95% CI	Child Onset (n = 583)	95% CI	Adult Onset (n = 280)	95% CI	Child Onset (n = 0)	95% CI
PJI rate	8.12%	5.78 to 11.01	2.18%	1.16 to 3.70	8.70%	5.77 to 12.49	NA	NA
Infection type	TB (myco) (n = 314)	95% CI	Bacterial (n = 706)	95% CI	TB (myco) (n = 9)	95% CI	Bacterial (n = 271)	95% CI
PJI rate	6.32%	2.97 to 10.82	4.54%	2.51 to 7.13	0.00%	NA	8.98%	5.95 to 12.88
Procedure	THA (n = 807)	95% CI	TKA (n = 213)	95% CI	THA (n = 230)	95% CI	TKA (n = 50)	95% CI
PJI rate	4.08%	2.36 to 6.23	8.62%	5.27 to 13.12	9.14%	5.83 to 13.49	6.91%	1.86 to 16.98

TJA, total joint arthroplasty; SA, septic arthritis; CI, confidence interval; PJI, periprosthetic joint infection; TB, tuberculosis; THA, total hip arthroplasty; TKA, total knee arthroplasty; NA, not available

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QUESTION 3: What indicators/metrics would compel a surgeon to perform resection arthroplasty and antibiotic spacer insertion, delaying the arthroplasty to a later date, in a patient with prior septic arthritis undergoing primary arthroplasty?

RECOMMENDATION: Patients with active septic arthritis or chronic osteomyelitis of the hip or knee may be best treated with a two-stage arthroplasty. Evidence would suggest a limited risk of infections recurrence following a one-stage arthroplasty in the presence of a quiescent septic arthritis.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 85%, Disagree: 11%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Although degenerative joint diseases are a common sequela of septic arthritis in a native hip or knee, the incidence of septic arthritis is relatively low. Therefore, orthopaedic surgeons are not regularly confronted with the difficult decision regarding the treatments of degenerative joint disease in patients with prior septic arthritis. Due to the low incidence, we are confronted with a paucity of literature to guide our treatment decisions.

In the reporting of outcomes, the literature has differentiated between active and quiescent septic arthritis/osteomyelitis of the hip or knee. Patients with quiescent septic arthritis/osteomyelitis often had a distant history of infections and the investigation of serum, synovial aspirate and imaging studies demonstrated no signs of active infections. Given the differentiation made in the literature, we have reviewed the two different hip and knee patient populations.

Among the reporting of total hip arthroplasties (THAs), seven publications with 98 hips and nine publications with 398 hips were identified as reporting on active or quiescent hip septic arthritis/osteomyelitis, respectively (Table 1). All reports of active hip infections were only treated with a two-stage arthroplasty, which demonstrated a 10.2% recurrence of infection. Unlike the active hip infections, all quiescent hip infections were treated with a one-stage arthroplasty with a 1.5% recurrence of infection.

Even fewer publications were available on total knee arthroplasties (TKA), which had seven publications with 46 knees and five publications with 89 knees reporting on active and quiescent knee septic arthritis/osteomyelitis, respectively (Table 2). Among the reports of active knee infections, all but three knees were treated with a two-stage arthroplasty demonstrating a 4.7% recurrence of infection, while the three knees treated with a one-stage arthroplasty had no recurrences. Similar to quiescent hip infections, all quiescent knee infections were treated with a one-stage arthroplasty and had a 4.5% recurrence of infection.

The literature suggests performing routine two-stage arthroplasty for active infections at the time of arthroplasty and one-stage arthroplasty for quiescent infections at the time of arthroplasty. Although the rates of infections are relatively low utilizing these parameters, there is conversely limited data about the failure rates after one-stage arthroplasty with an active infection and no data about two-stage arthroplasty for quiescent infections. As a result, it is possible that these recommendations could change with additional future research.

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TABLE 1. Publications reporting on active and quiescent hip septic arthritis/osteomyelitis

Lead Author, Year	Infection Classification (Active vs. Quiescent)	Procedure (One- vs. Two-stage)	Number of Hips	Average Follow-up Duration (Months)	Number of Infection Recurrence
Kim (2003)[1]	Quiescent	One-stage	170	119	2
Park (2005)[2]	Quiescent	One-stage	75	70	1
Lustig (2007)[3]	Quiescent	One-stage	17	72	1
Chen (2008)[4]	Active	Two-stage	28	77	4
Kim (2009)[5]	Quiescent	One-stage	62	156	1
Yoo (2009)[6]	Quiescent	One-stage	38	100	1
Gao (2010)[7]	Quiescent	One-stage	19	34	0
Bauer (2010)[8]	Active / Quiescent	Two-stage / One-stage	13 / 9	60	2 / 0
Huang (2010)[9]	Active	Two-stage	15	42	0
Fleck (2011)[10]	Active	Two-stage	10	28	1
Shen (2013)[11]	Active	Two-stage	5	40	0
Anagnostakos (2016)[12]	Active	Two-stage	16	45	3
Papanna (2017)[13]	Active / Quiescent	Two-stage / One-stage	11 / 7	70 / 72	0 / 0

TABLE 2. Publications reporting on active and quiescent knee septic arthritis/osteomyelitis

Lead Author, Year	Infection Classification (Active vs. Quiescent)	Procedure (One- vs. Two-stage)	Number of Knees	Average Follow-up Duration (months)	Number of Infection Recurrence
Böhler (2000)[14]	Active	One-stage	3	15	0
Lee (2002)[15]	Quiescent	One-stage	20	60	1
Nazarian (2003)[16]	Active	Two-stage	14	54	0
Bae (2005)[17]	Quiescent	One-stage	32	120	2
Kirpalani (2005)[18]	Active	Two-stage	5	38	0
Bauer (2010)[8]	Active / Quiescent	Two-stage / One-stage	17 / 14	60	2 / 1
Ashraf (2013)[19]	Active	Two-stage	2	30	0
Chen (2013)[20]	Quiescent	One-stage	22	Unreported	Unreported
Hochreiter (2016)[21]	Active	Two-stage	2	12	0

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QUESTION 4: Does a prior arthroscopy of the hip joint increase the risks of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing elective total hip arthroplasty?

RECOMMENDATION: There is no evidence to suggest that a prior arthroscopy of the hip increases the risk of subsequent SSIs/PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 81%, Disagree: 11%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

The use of hip arthroscopy for the treatment of various intra-articular or extra-articular problems has gained popularity during last decade [1,2]. Hip arthroscopy is known to be a safe and effective method for the treatment of femoroacetabular impingement (FAI) [3,4]. It is assumed, that the arthroscopic management of impingement or labral pathology will delay the process of joint degenerative disease. However, a considerable number of patients with both conservatively and arthroscopically-managed FAI eventually undergo total hip arthroplasty (THA) [5,6]. A second surgery, on a previously operated hip, could be complicated by scar formation and changes in neurovascular anatomy. In addition, potential contamination of the hip during hip arthroscopy could potentially predispose the patient to SSIs/PJIs after THA.

Several studies have evaluated the functional and clinical outcomes of THA after ipsilateral hip arthroscopy [7–12]. All of the studies on this subject were case-control studies, largely focusing on functional and clinical outcomes. The available studies did not have sufficient patient numbers to determine the risk of SSIs/PJIs following previous arthroscopy. Zingg et al. [7] compared three groups of patients. One group consisting of 18 patients who underwent THA after previous ipsilateral hip arthroscopy, compared with two control groups with a minimum of one-year follow-up. One control group received identical approach and implants; and the other a paired group matched for age, Body Mass Index (BMI) and Charnley categories. In their case cohort, only one patient had a superficial wound infection due to a suture granuloma that resolved with antibiotic therapy. They reported that previous hip arthroscopy would not negatively influence the performance or short-term clinical outcome of THA.

Nam et al. [12] compared 43 patients who received hip resurfacing arthroplasty following previous hip arthroscopy to a 1:2 matched group of 86 controls. Various clinical and functional outcomes were evaluated at different time points of six weeks, three months, six months, one year, and most recent follow-up visits. No ultimate differences were reported in functional scores, range of motion or complications, including infection at final follow-up.

Haughom et al. [10], evaluated 42 hips who underwent THA after a previous hip arthroscopy at a mean follow-up of 3.3-years and compared them to an age, sex and BMI (1:2) matched cohort of primary THAs. No significant difference was observed in postoperative Harris Hip Scores (HHS), rates of complications or revisions. One patient in each group had a PJI and underwent a subsequent revision.

Charles et al. [9], compared 39 patients who underwent THAs after hip arthroscopy to a 1:1 group of patients matched for age, sex and body mass index who underwent THA without prior hip arthroscopy. The groups had no statistically significant differences in terms of postoperative superficial or deep periprosthetic infections at a minimum 1-year follow-up (mean 52 months).

In a recent study, Perets et al. [11], compared 35 THA patients with a history of prior hip arthroscopy to a group of 1:1 matched controls. The matching criteria were age, sex, body mass index, surgical approach and robotic assistance. They evaluated the Harris Hip Scores (HHS), Forgotten Joint Score-12, Visual Analog Scale (VAS), satisfaction, postoperative complications, and reoperation rates following a minimum two-year follow-up. In the case group, 2 patients (5.7%) had minor infections which were managed nonoperatively compared to zero infections/complications in the control

group. Although the prior arthroscopy group had higher rates of both complications (n = 5, 14.3%) and reoperations (n = 4, 11.4%), only the difference in total complications approached marginal significance (p = 0.054). Complications consisted of urinary tract infection, numbness around the incision, minor infection and allergic reaction to sutures.

With the current evidence available, we cannot conclude that a prior hip arthroscopy exposes patients undergoing THAs to a higher risk of infections. There is a need for studies with greater sample sizes to further explore this important question.

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QUESTION 5: Does a prior arthroscopy of the knee increase the risk of subsequent surgical site infections/periprosthetic joing infections (SSIs/PJIs) in patients undergoing elective arthroplasty?

RECOMMENDATION: There is no evidence to suggest that a prior arthroscopy of the knee increases the risk of subsequent SSIs/PJIs in patients undergoing total knee arthroplasty (TKA).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 81%, Disagree: 12%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Arthroscopy in the degenerate knee is not warranted, but it has been frequently performed over the years. Controversial indications have included young adults with degenerative joint disease to delay TKA [1,2] and for elderly patients for alleviating pain [3,4]. Knee arthroscopy can be appropriately used for loose body removal, meniscectomy, chondroplasty, ligamentous reconstruction and as a diagnostic tool prior to unicondylar knee arthroplasty [5]. The rate of TKA following knee arthroscopy within one year is 10-12% [6–8], and those following ligamentous knee surgery have a higher risk of earlier osteoarthritis requiring TKA [9]. Studies have shown increased risks of revisions and PJIs after TKAs in patients with previous open-knee procedures [10–12], but the evidence for knee arthroscopy is conflicting.

Piedade et al. evaluated the outcomes and complications of TKAs in two retrospective cohort studies [11,13]. The first was a cohort of 1,119 primary TKAs with no previous surgery compared to 60 primary TKAs with a prior history of arthroscopic debridement and a minimum follow-up of two years. Two patients in the arthroscopy group (3%) and 14 patients in the primary TKA group (1.25%) had subsequent PJIs. Although this finding was not statistically significant, the total complication, reoperation and revision TKA rates were higher in the prior arthroscopic group. In addition, the authors found no correlations between arthroscopy-TKA intervals (mean of four years) and complications or failures [11]. The second study did not specify the rates of infections [13]. When looking at general outcomes, Issa et al. reported no negative outcomes (function, survivorship and revision) following TKA after prior knee arthroscopy [14].

The time interval between arthroscopy and TKA is also important as was shown by Werner et al. [8], who evaluated the associations of knee arthroscopy prior to TKA with postoperative complications (infection, stiffness and venous thromboembolism) from a national database. Three cohorts were compared with each other and with an age-matched cohort. The three cohorts were: TKA within 6 months (n = 681), between 6 to 12 months (n = 1,301) and between 1 to 2 years after knee arthroscopy (n = 1,069). They reported that TKAs performed within 6 months were associated with increased rates of postoperative infection, stiffness and venous thromboembolism.

Viste et al. [6], evaluated long-term Knee Society Scores (KSS), survivorships and complications of 160 TKA patients with prior knee arthroscopy (excluding ligamentous reconstruction) to a 1:2 matched control group of 320 primary TKAs with no prior surgery. The mean follow-up was nine years and the mean interval between arthroscopy and TKA was five years. Although PJIs were found in two controls and three arthroscopy cases, these findings were not statis-

tically significant (p = 0.2). In addition, there were no significant differences between the two groups regarding complications, ranges of motion and revisions. Twenty-five patients (15.6%) had a knee arthroscopy within one year of their TKA during which time there were no increased risks of infections, other complications, reoperations or revisions.

A national registry database study of 64,566 primary TKAs found that prior ligament reconstruction (odds ratio (OR) = 1.85) was an independent risk factor for PJIs at 12 months in multivariate analysis, with no details of whether this was open or arthroscopic. Interestingly, meniscectomy was an independent protective factor (OR = 0.66) in the same study [15].

We conclude that a prior arthroscopy of the knee does not seem to increase the incidence of subsequent SSIs/PJIs following TKA. However, most studies on this subject are retrospective with small cohorts, making it difficult to accurately assess the risk of subsequent infection. Only one study showed an increased rate of infection within six months, and this has not been repeated in the literature. Further studies are required, and until then, surgeons may wish to consider delaying TKA for at least six months post-arthroscopy to minimize any risk that may exist, particularly in high-risk patients.

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QUESTION 6: Do patients undergoing outpatient total joint arthroplasty (TJA) have a higher incidence of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: No. Patients undergoing outpatient total joint arthroplasty do not have a higher incidence of SSIs/PJIs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 83%, Disagree: 8%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

PJIs are a serious condition with a high impact on patients and surgeons. The leading cause of 30-day readmission after total knee arthroplasty (TKA) is deep or superficial SSIs, which accounts for 12.1% of unplanned readmissions [1]. SSIs accounted for 23.5% of unplanned readmissions in total hip arthroplasty (THA) patients, just behind hip dislocations. Lovett-Carter et al. reported that the length of hospital stay (LOS) is implicated as a risk factor for SSIs or PJIs, among other factors such as comorbidities, gender and duration of procedure [2]. Outpatient TJA has not been seen to be a concern in the literature.

In a study that evaluated 58,000 standard-stay, primary THA patients, the deep SSI rate was seen to be 0.2% [3]. In a more recent study, Lovett-Carter et al. evaluated outpatient 742 THAs and 816 TKAs and observed 0 and 3 (0.36%) SSIs, respectively [2].

Nelson et al. revised the collected data from the 2005 to 2014 American College of Surgeons National Surgical Quality Improvement Database (ACS NSQIP) of patients who underwent THA as outpatient (LOS 0 days) or inpatient (LOS 1-5 days). A total of 63,844 THA patients were identified of which 420 (0.66%) were outpatients. They concluded that patients undergoing outpatient THA were not at an increased risk of 30-day adverse events or readmissions or infections compared to inpatient procedures. Deep SSIs in patients with LOS between 1 to 5 days was 0.23% and in outpatients was zero (p = 0.319). The rate of superficial SSI was 0.64 vs. 0.48% (p = 0.821), respectively [4].

Springer et al. compared 30-day hospital readmission rates for patients undergoing outpatient and inpatient TJAs. They evaluated if LOS impacted hospital readmission rates and unplanned care

TABLE 1. ACS NSQIP database comparison of complications within 30 days of surgery between the outpatient and inpatient TJA groups [7]

SSI	Outpatient: N = 1,220	Inpatient: N = 168,186
Superficial	6 (0.5%)	1.053 (0.6%)
Deep	4 (0.3%)	354 (0.2%)

episodes. The group found that there was only 1 case of hospital readmission out of 137 patients due to infection in the outpatient group (0.7%), and none of the 106 patients in the inpatient group had any unplanned care episodes [5]. They concluded that no statistical differences were seen in 30-day readmission or unplanned care episode. Kolisek et al. compared the results of two selected matched cohorts of 64 patients who underwent TJA during the same period, and found two cases of SSIs in the inpatient group vs. zero in the outpatient cohort [6]. Courtney et al. determined that the complications associated with outpatient vs. inpatient TJA seen in the ACS NSQIP database were not significant, specifically in superficial and deep SSIs [7].

When comparing costs, complications and mortality between outpatient TKA patients and those who had a 3 to 4 night hospital stay, Lovald et al. determined that the SSI rate was not different at 1.9 and 2.0% respectively [8]. Furthermore, Goyal et al. performed a multicenter, randomized control study, comparing patients undergoing THA as inpatients (108) and outpatients (112). They showed no differences in SSI rates, 0.92% and 0.89% respectively, at four weeks follow-up [9]. Klein et al. reported 5 infections (0.9%) in 549 THAs as outpatient with a follow-up of 90 days [10]. Berger et al., with the same follow-up, evaluated 25 unicondylar knee arthroplasties and 86 TKAs as outpatient surgeries and found only one irrigation and debridement [11]. Bovonratwet et al. compare 956 inpatient TKAs with 642 outpatients in a follow-up of 30 days and found SSI rates of 0.85 and 0.78% respectively [12].

Only one retrospective, database study by Arshi et al. showed different findings than the studies mentioned above. They compared 4,391 outpatient TKAs vs. 128,951 inpatient TKAs and saw a significant difference in SSI incidences of 1.21% and 0.91% respectively [1]. They concluded that data from a private insurance database demonstrated higher risks of perioperative surgical and medical complications, including, component failure, SSI, knee stiffness and deep vein thrombosis. However, it should be noted that this study did have selection bias for their patients, and was extracted from a database that could potentially add bias.

Basques et al. reviewed the ACS NSQIP database for comparisons between same-day discharge and inpatient hospitalizations of elective hip and knee arthroplasty cases in terms of postoperative complications and 30-day readmission rates [13]. This study was comprised of 1,236 same-day surgery cases that were identified from their institution, and matched to the same number of cases from the database. Same-day cases were found to have higher readmission rates and returns to the operating room. In particular, infections were the most common cause for readmissions and returns to the operating room. On the other hand, the inpatient group had a higher incidence of thromboembolic events. These higher readmission rates were seen specifically for patients in the same-day surgery TKA group. The risk factors for 30-day readmissions following same-day procedures include BMI > 35 kg/m^2, diabetes and age > 85 years.

In conclusion, based on available data, performing TJA in an outpatient setting does not seem to predispose patients to a higher incidence of SSIs/PJIs.

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1.3. PREVENTION: ANTIMICROBIALS (SYSTEMIC)

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QUESTION 1: What is the most appropriate perioperative prophylactic antibiotic (agent, route and number of doses) for patients undergoing primary total joint arthroplasty (TJA) to reduce the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: The most appropriate perioperative prophylactic antibiotic is a first or second-generation cephalosporin (i.e., cefazolin or cefuroxime) administered intravenously within 30 to 60 minutes prior to incision as a single- and weight-adjusted dose.

LEVEL OF EVIDENCE: Strong

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

RATIONALE

The optimal prophylactic antibiotic should be a bactericidal agent against the most common organisms responsible for causing SSIs/PJIs. The agent must be present within the tissues at the time of initial incision, with adequate serum concentrations above the minimum inhibitory concentration (MIC) and should be maintained during the procedure [1,2]. A first- or second-generation cephalosporin (i.e., cefazolin or cefuroxime) can be used for routine perioperative prophylaxis with excellent distribution and cost effectiveness. The American Academy of Orthopaedic Surgeons (AAOS) currently recommends the use of either of these two agents in patients undergoing any orthopaedic procedure including TJA [3]. Prophylaxis should target the most common organisms (i.e., *Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli,* and *Proteus*) while avoiding unnecessary broad-spectrum therapies [4]. Glycopeptides, such as teicoplanin and vancomycin, have also been introduced as reasonable alternatives, although they have a narrower spectrum of action with minimal activity against gram-negative bacteria [5–7].

Vancomycin is selectively used in patients, such as nursing home residents and healthcare workers, who are MRSA carriers or at high-risk of MRSA colonization. In patients with documentation or suspicion of an allergy to cephalosporins, clindamycin can also be utilized and should be administered within one hour of the surgical incision. Vancomycin should be started two hours prior to incision due to the extended infusion time [8,9]. Although alternative agents such as vancomycin have been suggested in cases of allergies to cephalosporins, these have been associated with higher rates of SSIs if used alone [10–12]. In the study by Courtney et al., the authors reported that the addition of vancomycin to the prophylactic antibiotic regimen does not decrease the rates of SSIs, when compared with cefazolin alone, and could increase the risks of adverse effects [12]. Without clear evidence, the superiority of dual-antibiotic prophylaxis in prevention of infection should be carefully considered.

Bosco et al. [13] evaluated the increasing prevalence and virulence of gram-negative pathogens as these were the causative pathogens in up to 30% of infections in total hip arthroplasty (THA). They instituted the Expanded Gram-Negative Antimicrobial Prophylaxis (EGNAP) for hip arthroplasty patients. Two groups were compared in terms of SSI rates; one group did not receive weight-based, high-dose gentamicin while the second group did. The reported rates were 1.19 vs. 0.55% after EGNAP was implemented ($p = 0.05$). On a different study, Tan et al. [14] specifically evaluated the influence of comorbidities and use of perioperative antibiotics in 1,022 patients with PJIs to determine the influence of comorbidities on organism profile. They found that no comorbidities were associated with an increased rate of gram-positive or gram-negative infections. Their results support the current recommendations of a universal antibiotic prophylaxis protocol rather than an antibiotic regimen individualized to a patient's comorbidities.

Malhas et al. [15] examined microbiological results from hip and knee revisions from 2001 to 2010. Antibiotic resistance patterns were evaluated on *Staphylococcus aureus* (SA) and coagulase-negative *Staphlococcus* (CNS) cultured from regional pan-speciality sources. A total of 72 revisions in 67 patients were included. The most common organisms were SA (36%) and CNS (35%). Resistance to methicillin was 72 for CNS vs. 20% for SA and resistance to gentamicin was 40% for CNS vs. 4% for SA. Among all regional (background pan-speciality) cultures, SA resistance to methicillin fell from 32 to 16% from 2006 to 2010 with no change in gentamicin resistance at 3%. During the same period, resistance of CNS to methicillin and gentamicin increased from 63 to 70% and 32 to 47%, respectively. The prophylaxis regimen prior to 2008 was cefuroxime, and after 2008 was gentamicin and flucloxacillin.

Other Agents

Flucloxacillin and gentamicin: Torkington et al. [16] investigated bone penetration of intravenous antibiotic prophylaxis with flucloxacillin (2 gm) and gentamicin (3 mg/kg) single doses during hip (18 patients) and knee (21 patients) arthroplasty, and their efficacy against *S. aureus* and *S. epidermidis*. This study demonstrated that the intravenous antibiotic prophylaxis combination of flucloxacillin and gentamicin achieved adequate concentrations in bone against the common causative organisms in total knee arthroplasty (TKA) and total hip arthroplasty (THA) PJIs, adding to the available evidence to support its use.

Teicoplanin: Four randomized controlled trials provided strong evidence for the use of a single dose of 400 mg of teicoplanin at induction in selected cases [17,18]. Although there is no evidence to suggest that higher doses or prolonged courses of treatments result in fewer SSIs, studies have shown that this dose may be inadequate for patients weighing over 70 kgs [19].

Sulbactam-ampicillin: Yuasa et al. [20] compared the incidence of SSIs with two doses of sulbactam-ampicillin after THA: 1.5 and 3 grams. They found a global decrease in SSIs in the 3 gm dose group from 2.91 to 1.08% ($p = 0.268$), and in deep infection from 1.2 to 0% ($p = 0.231$).

Cloxacillin vs. clindamycin: Robertson et al. compared the risks of PJIs between the use of cloxacillin and clindamycin as perioperative antibiotics in 80,018 TKAs. The risk of failure leading to revision due to PJI was higher with clindamycin compared to cloxacillin (risk ratio (RR) = 1.5, 95% confidence interval (CI): 1.2 to 2.0; $p = 0.001$). Clin-

damycin inhibits bacterial protein synthesis by binding to bacterial 50S ribosomal subunits and it may be bacteriostatic- or bactericidal-based on the organism and drug concentration. Cloxacillin is in the beta-lactam category and works by binding to specific penicillin-binding proteins located inside the bacterial cell wall which inhibit cell wall synthesis. The primary reason for using clindamycin as a perioperative prophylaxis antibiotic is a reported allergy to penicillin. Even though between 5 and 10% of hospitalized patients report allergy to penicillin, most have negative results when tested for type-I hypersensitivity [21].

Dose

Current guidelines and studies recommend giving universal antibiotic prophylaxis to all TJA patients regardless of their medical conditions or immune status [2,3,14]. We did not identify studies that showed consistent reports on prophylactic dosage. Clinical practice guidelines, based on available evidence and expert opinion, recommend increasing the single preoperative prophylactic antimicrobial agent dose for select prophylactic antimicrobial agents in overweight and obese patients. For cefazolin, recommendations are to administer 2.0 gm for patients weighing > 60-80 kg and 3.0 gm if > 120 kg. For aminoglycosides, dosing is calculated using the patient's ideal body weight plus 40% of the difference between the actual and ideal body weight. Vancomycin should be dosed at 15 mg/kg. The goal of dosing is to achieve a safe and effective tissue concentration of the drug that sufficiently exceeds the concentration needed to inhibit the growth of most colonizing skin flora at the time of surgical incision [2,7].

Angthong et al. [22] found that IV cefazolin at a dose of 2 gm produced greater intraosseous concentrations overall than a dose of 1 gm. However, the higher intraosseous concentrations did not correlate with higher inhibitory effects. A second study demonstrated that biofilm formation could develop for up to 1–2 days [12]; therefore, hypothetically, the higher dose (2 gm) of cefazolin might be more beneficial than the lower dose of 1 gm [22].

Redosing: Moderate-quality evidence suggested no benefits of intraoperative antibiotic redosing. Clinical practice guidelines, based on a review of the evidence and expert opinion, recommend prophylactic antimicrobial agent redosing in cases of prolonged procedures (when the procedure exceeds the half-life of the prophylactic antimicrobial agent or is longer than 3 to 4 hours) and in patients with major blood loss (> 1,500 ml) or extensive burns. Redosing should also be performed at intervals of 1 to 2 times the prophylactic antimicrobial agent half-life, starting at the beginning of the preoperative dose [2].

Route

The best route to deliver antibiotics prior to total joint arthroplasty is considered to be intravenous in order to reach levels above MIC. Therapeutic concentrations should be maintained for the duration of the surgical procedure. Recent publications have suggested alternate routes such as intraosseous administration, although further research is required [1]. Irrigation solutions with antibiotics have also been used with little or no evidence. Among the few available low-evidence studies, Whiteside reported his experience in 2,293 arthroplasties using an irrigation solution of normal saline with vancomycin 1,000 mg/l and polymyxin 250,000 units/L at 2 L/hour. No patients required readmission for primary infection or further antibiotic treatment [23]. However in a meta-analysis study evaluating the use of topical antibiotic in colo-rectal surgery, no benefit was identified when used in conjunction with systemic antibiotics [1]. At present, the use of topical antibiotics, in conjunction with systemic antibiotics for prophylaxis in total joint arthroplasty, remains unproven.

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QUESTION 2: What are the appropriate weight-adjusted prophylactic antibiotic dosages?

RECOMMENDATION: The recommended weight-adjusted doses of antimicrobials for prophylaxis of hip and knee arthroplasty in adults are shown in Table 1.

TABLE 1. Recommended weight-adjusted doses of antimicrobials for prophylaxis of hip and knee arthroplasty in adults

Antimicrobial	Recommended Dose	Re-dosing Interval
Cefazolin	2 gm (consider 3 gm if patient weight ≥ 120 kg*)	4 hours
Vancomycin	15-20 mg/kg*	Not applicable
Clindamycin	600-900 mg#	6 hours

*Actual body weight.
#No recommended adjustment for weight.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

We performed a systematic review in order to examine the literature and determine appropriate weight-adjusted prophylactic antibiotic doses for the prevention of infections after hip and knee arthroplasties. The nature of the question and the lack of high-quality evidence did not allow a formal systematic review. We searched for larger comparative studies or systematic reviews where different doses of antibiotics or different antibiotics are being compared or smaller prospective pharmacokinetic/tissue penetration studies where antibiotics doses are recorded. We included studies examining systemic (not local) antimicrobials and where the antimicrobial was given for a primary or revision hip or knee arthroplasty procedure and no other procedures (e.g., dental procedure) with a prosthetic joint *in situ*.

Perioperative antimicrobial prophylaxis for patients undergoing orthopaedic procedures is routinely administered and is believed to be one of the most important steps for prevention of surgical site infections/periprosthetic joint infections (SSIs/PJIs). Cephalosporins are believed to be the most effective prophylactic agents for patients undergoing orthopaedic procedures as they have excellent bone penetration, bioavailability and a relatively extended half-life. However, in patients with allergies, a range of antimicrobials may be utilized that includes vancomycin and clindamycin.

The American Society of Health-System Pharmacists (ASHP) clinical practice guidelines provide important information regarding antimicrobial prophylaxis in surgery [1]. Doses of antimicrobials commonly used for surgical prophylaxis can be found in these guidelines. No high-quality randomized trials are investigating the safety or efficacy in preventing surgical infections of different doses of prophylactic systemic antimicrobials for surgery, including joint arthroplasty. The first International Consensus Meeting in 2013 recommended that perioperative antimicrobial prophylaxis be weight-based. These recommendations were based on the notion that the dose of antibiotic administered directly influences the serum levels of the given antimicrobial with inadequate serum levels of the antimicrobial being considered detrimental.

Serum and tissue concentrations of antimicrobials given at standard doses may not be adequate in obese patients due to various factors [2]. Pharmacokinetic studies have shown that tissue levels of cefazolin below the minimal inhibitory concentration (MIC) of common pathogenic organisms are found in body tissues near the end of surgery with a 1 gm dose [3,4]. In one small, prospective study on obese patients, a 2 gram dose of cefazolin was associated with a lower surgical site infection rates than a 1 gm dose [4]. A 2 gm dose likely achieves appropriate local surgical tissue levels, including in bone, in normal size patients [5]. However, in one study with morbidly obese patients, a 2 gm dose was associated with levels below pathogen MICs of cefazolin [6]. Given the finding of these studies, as well as the low cost and favorable safety profile of cefazolin, weight-based dosing of prophylactic cefazolin has been recommended as part of the ASHP clinical practice guideline for antimicrobial prophylaxis in surgery [1]. In this guideline, 2 gm of cefazolin is recommended as a standard dose and 3 gm for patients weighing 120 kgs or greater. Subsequent small studies [7,8], including a small randomized controlled trial [9], have compared tissue levels of 2 gm with 3 gm of cefazolin in obese women undergoing caesarean section. These have shown higher tissue levels in patients receiving 3 gm; however, 2 gm doses generally exceeded the MIC of common pathogens. Given the lack of evidence showing a clear benefit in tissue penetrations or reduced infection rates, we recommend that a 2 gm dose of cefazolin is appropriate for most patients; however, given the limited toxicity, a 3 gm dose can be considered in patients ^{3} 120kg as per ASHP guidelines.

There is some evidence to suggest that vancomycin may be more likely to achieve therapeutic serum levels with weight-based dosing of 15 to 20 mg/kg compared with a standard dose (often 1 gm) when given for surgical prophylaxis without an increased risk of renal impairment. Patients receiving appropriate weight-based dosing may have a lower rate of methicillin-resistant *Staphylococcus aureus* (MRSA) infection, however, there is no evidence suggesting an overall lower rate of infection [10–12]. In addition, weight-based dosing rather than a fixed 1 gm dose has been recommended for total joint arthroplasty [10,11]. Kheir et al. reported that a fixed 1 gm dose was administered in 94% of total joint arthroplasties with 64% (1105/1726) of these patients being underdosed. Furthermore, the authors found that weight-based dosing achieved higher levels of vancomycin at all points during surgery without increasing nephrotoxicity and acute kidney injury [10].

There are no studies comparing clinical or pharmacokinetic outcomes with different doses of clindamycin for surgical prophylaxis. Older pharmacokinetic studies show a good penetration of clindamycin into surgical tissues including bone [13–15]. Based on serum levels after intravenous administration, this suggests that commonly used doses of 600 mg or 900 mg should exceed the MIC of most relevant pathogens [1,15].

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QUESTION 3: Is one dose of preoperative antibiotic adequate for patients undergoing total joint arthroplasty (TJA)?

RECOMMENDATION: Despite the current guidelines from the Centers for Disease Control and Prevention (CDC) advocating for a single dose of perioperative antibiotics, these studies are underpowered and primarily in specialties outside orthopaedics. From the limited evidence available, it appears that a single perioperative dose of antibiotics, compared to multiple doses, does not increase the rate of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs). A randomized prospective study in patients undergoing elective arthroplasty is underway that should answer this question definitively.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 7%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Perioperative antibiotic prophylaxis remains an important strategy for minimizing one of the most devastating complications following TJAs, PJIs [1,2]. All current guidelines recommend the use of perioperative antibiotics [3–7] (Table 1). For arthroplasty, the costs and morbidities associated with PJIs have led to abundant research to reduce the rate of postoperative infections. To this end, perioperative antibiotics are widely used; however, hospital protocols vary from a single preoperative dose to several days of postoperative prophylaxis. Many surgeons administer antibiotics for a total of 24 hours as this is the maximum time period recommended by several current guidelines. However, there was a recent change in the guidelines provided by the World Health Organization (WHO) and CDC. They recommend against the administration of antibiotics in the postoperative period and that only a single preoperative antibiotic be administered, largely due to fears of increased bacterial resistance and side effects of unnecessarily prolonged antibiotics [4,5]. The 2017 CDC Guidelines issued this statement as a strong recommendation with high-quality evidence. However, the limited literature in arthroplasty cannot support this recommendation.

A recent systematic review and meta-analysis by Thornely et al. explored whether or not a single preoperative antibiotic dose is adequate for arthroplasty patients [8]. Their review returned four randomized controlled trials (RCTs) [9–12] with a total of 4,036 patients. In patients receiving postoperative prophylaxis, the infection rate was 3.1% (63/2055), compared to the rate (2.3%) of a single preoperative dose (45/1981). They concluded that postoperative antibiotics did not reduce the rates of infections; however, they reported that the quality of evidence was very low. Among the available RCTs, three include teicoplanin as a single dose treatment, which is currently unavailable in the United States [10,13,14]. Heydemann et al. randomized 211 patients to a single dose vs. 48 hours of nafcillin or cefazolin; no deep infections were seen in either cohort [9]. Ritter et al. compared a single preoperative dose of cefuroxime to 24 hours of postoperative prophylaxis in a small RCT of 196 patients, and found no postoperative infections in either group [11]. Lastly, Wymenga et al., in a multicenter RCT of 3,013 patients, compared a single preoperative dose of cefuroxime to a group receiving 3 total doses and found no significant differences in infections between groups. These

authors, however, recognize that their sample sizes were too small to detect a difference given the infrequency of PJIs and recommended continued use of postoperative prophylaxis until larger studies could be performed [12]. Other literature has been retrospective in nature, including reviews by Tang et al. [15] and van Kasteren et al. [16], each of which had < 2,000 patients and found no differences in infection rates between groups. The largest retrospective review by Engesaeter et al. showed a significantly higher revision rate with a single dose compared to four doses given on the day of surgery. The higher revision rate was partially caused by infections [17]. While the majority of studies are underpowered, a retrospective study by Tan et al. demonstrated no differences in 90-day or 1-year PJIs in the 4,523 patients that received a single dose of antibiotics compared to 16,159 patients that received 24 hours of antibiotics. Throughout all preoperative risk groups, however, patients with 24 hours of antibiotics demonstrated a trend toward a higher rate of acute renal failure.

It is important to recognize the different antibiotics used in each study noted above, as well as the small sample sizes. Furthermore, the meta-analysis performed by the CDC predominantly includes surgical interventions of the trunk without hardware retention (including vascular surgery, cardiothoracic surgery, general surgery, as well as ear, nose and throat). For surgeries of the extremity with retained implants, however, the evidence is more limited and consists of small RCTs or retrospective reviews without sufficient power to detect a statistical differences [13,14,18–25]. Among them, Gatell et al. did find a significant reduction in the rates of infections compared to a single preoperative dose for patients with retained metal implants [24]. These studies were also performed predominantly in the 1990s and early 2000s and modern antibiotics may have a different result. Given the devastating outcomes of PJIs for patients, we neither agree nor disagree with the CDC recommendations that antibiotics should not be provided postoperatively until sufficiently powered evidence can be provided through a multicenter RCT that is adequately powered and is considering the low event rate of infection in total joint arthroplasty. While future studies may show that there are no differences in single versus multiple doses of perioperative antibiotic prophylaxis, the current literature does not support this strong conclusion.

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TABLE 1. Guidelines for perioperative antibiotic prophylaxis

	Organization										
Recommendation from Guidelines	BOA 2012	AAOS 2014	SAOA 2016	ACS 2016	SCIP 2011	IHI 2012	ASHP 2013	SIGN 2014	WHO 2016	CDC 2017	NICE 2017
Appropriate antibiotic selection	√	√	√	√	√	√	√	√	√	√	√
Administration within 1 hr before surgical incision	√	√	√	√	√	√	√	√	√	√	√
Discontinuation after incision closure	–	–	–	No	–	–	–	–	√	√	–
Discontinuation within 24 h	Debatable	√	√	Unknown	√	√	Debatable	–	–	–	–

BOA, British Orthopaedic Association [1]; AAOS, American Academy of Orthopaedic Surgeons [2]; SAOA, South African Orthopaedic Association [3]; ACS, American College of Surgeons [4]; SCIP, Surgical Care Improvement Project [5]; IHI, Institute for Healthcare Improvement [6]; ASHP, American Society of Health-System Pharmacists [7]; SIGN, Scottish Intercollegiate Guidelines Network [8]; WHO, World Health Organization [9]; CDC, Centers for Disease Control and Prevention [10]; NICE, The National Institute for Health and Care Excellence [11]

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QUESTION 4: Should patients undergoing outpatient total joint arthroplasty (TJA) receive additional postoperative prophylactic antibiotics?

RECOMMENDATION: Despite the current guidelines from the Centers for Disease Control and Prevention (CDC) advocating for a single dose of perioperative antibiotics, the studies utilized to form these guidelines are underpowered and primarily in specialties outside orthopaedics. The limited evidence suggests that a single perioperative dose of antibiotics, compared to multiple doses, does not increase the rates of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs). A randomized prospective study in patients undergoing elective arthroplasty is underway, which should help answer this question definitively.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Administration of prophylactic antibiotics during TJA surgery has been demonstrated to be an important step in the prevention of SSIs and PJIs. During the early years of arthroplasty, prophylactic antibiotics for a few days postoperatively was routine. Over the last decade or so, there has been a movement towards reducing the amount of prophylactic antibiotics administered to TJA patients. Currently, antibiotics are administered to patients undergoing primary TJA for a period of 24 hours. The number of doses of antibiotics that need to be administered to TJA patients is not known.

In recent years, and with the increase in popularity of outpatient TJA, many patients undergoing primary TJA may only receive a single dose of antibiotics. It is not known if a single dose of antibiotics may predispose these patients to higher incidences of SSIs/PJIs. Recent guidelines for prevention of SSIs issued by the World Health Organization (WHO) and the CDC recommend against the administration of additional postoperative antibiotics [1–3]. The recommendation by these organizations is in an antibiotic stewardship practice intended to limit liberal use of antibiotics that can result in the emergence of antimicrobial resistance and also expose patients to adverse effects associated with administration of prolonged antibiotics [2,4,5]. Although the CDC Guidelines issued this statement as a strong recommendation with high quality evidence, there is limited literature in arthroplasty to support this recommendation.

A systematic review and meta-analysis by Thornley et al. has examined the issue of number of doses of antibiotic prophylaxis following TJA. The analyses revealed that the incidence of infections was 3.1% (63/2055) in patients receiving multiple doses of antibiotics compared to an infection rate of 2.3% (45/1981) in patients receiving a single dose of antibiotics [6]. They concluded that postoperative antibiotics did not have additional benefits in reducing the rate of infections. The authors of the systematic review did acknowledge that the quality of evidence related to this subject in TJA is low. Of the four available randomized controlled trials, three include teicoplanin which is currently unavailable in the United States [7–9]. Furthermore, studies are usually underpowered with one randomized trial enrolling only 196 patients when comparing a single dose of cefuroxime to 24 hours of prophylaxis [10]. In addition, Wymenga et al. compared a cohort of patients who received a single preoperative dose of cefuroxime to a cohort who received 3 total doses in 3,013 patients and found no significant differences in infections between the two groups [11]. However, the authors recognized that their sample size was too small to detect a difference given the infrequency of PJI and recommended continuing the use of postoperative prophylaxis until larger studies could be performed [11]. Additionally, in a national registry study, Engsaeseter et al. demonstrated higher revision rates in patients receiving a single dose of antibiotics compared to four doses given on the day of surgery [12].

Lastly, a retrospective study by Tan et al. demonstrated no difference in the 90-day or 1-year PJIs in 4,523 outpatient TJA patients that received a single dose of antibiotics compared to 16,159 patients that received 24 hours of antibiotics, regardless of the patient's preoperative risk of PJIs [13].

When comparing infection rates between outpatient and inpatient total joint arthroplasty, the majority of the literature demonstrates no difference in the rate of postoperative infection. In a large retrospective review of the PearlDiver Database, Arshi et al. found that patients who underwent outpatient TKA demonstrated an increased risk of prosthesis explantation (adjusted odds ratio (OR) 1.35, 95% confidence interval (CI): 1.07-1.72) as well as irrigation and debridement (adjusted OR 1.50, 95% CI: 1.29-1.77) compared to inpatients [14]. Despite these findings, multiple large national database studies have demonstrated no difference in postoperative infection between outpatient and inpatient TJAs [15–18].

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QUESTION 5: Does extended prophylactic antibiotics therapy for patients undergoing aseptic revision help reduce the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: In the absence of concrete evidence, we recommend the use of routine antibiotic prophylaxis (maximum 24 hours) for patients undergoing revision arthroplasty as long as the infection has been properly ruled out prior to surgery.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 81%, Disagree: 15%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Infections are a common cause of failures post aseptic revisions, occurring after 5 to 9% for total knee arthroplasties (TKAs), and 1.35 to 17.3% for total hip arthroplasties (THAs) [1–6]. One of the modalities used to prevent SSIs and/or PJIs after arthroplasty is administration of prophylactic antibiotic therapy [7–9]. Considering the high rate of SSIs and PJIs after revision arthroplasties, one can argue that extended prophylaxis for longer than 24 hours may be indicated in these types of surgeries. Several studies conducted in primary TKA and THA, indicate no difference in the rate of SSI in patients who received prophylaxis for 24 hours and in those who received it for longer than 24 hours [10–14].

A comprehensive literature search was performed to identify studies evaluating the potential role of extended antibiotic prophylactic therapy following aseptic revision arthroplasty. A single retrospective study conducted by Claret et al. on 341 patients undergoing revision arthroplasty was identified [15]. The authors compared the rate of PJI after changing their local protocol from administering teicoplanin and ceftazidim before surgical incision to doing so again two hours after as an antibiotic prophylaxis (2007–2010) prolonging this regimen until the fifth day after revision surgery (2010–2013). Several criteria concerning inflammatory markers, imaging and synovial fluid analysis were performed to

rule out infection prior to revision surgery. They observed that the PJI rate, occurring within three months after revision surgery, was lower in the long prophylaxis group compared to the short prophylaxis group (2.2% vs. 6.9%, p = 0.049). In addition, prolonged antibiotic prophylaxis was the only variable independently associated with a lower rate of PJI in their analysis (odds ratio (OR): 0.27, 95% confidence intervals (CI): 0.07–0.99). These data suggest that there might be a protective effect of prolonging antibiotic prophylaxis. However, although no other protocol modifications were made during the study period according to the authors, bias cannot be completely ruled out due to the retrospective nature of the study, especially as diagnostic methods to rule out an infection prior to revision surgery have been improved over recent years. Thus, there is a need for a randomized controlled trial that can examine this question. The PARITY trial, an international prospective randomized controlled trial currently conducted in the field of orthopaedic oncology, may provide us with additional evidence about the potential benefit of extended antibiotic prophylaxis in high-risk patients undergoing joint arthroplasty [16].

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QUESTION 6: Should duration and the type of antibiotic prophylaxis be altered in patients with a prior periprosthetic joint infection (PJI)?

RECOMMENDATION: Antibiotic prophylaxis should be tailored in patients with prior PJIs who are undergoing another subsequent elective primary or revision joint arthroplasty. Antibiotic prophylaxis should cover the initial causative organism(s) as well as the most common pathogens that can cause PJI with either single or dual antibiotics.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 6%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Patients with prior PJIs have a significantly higher risk for PJI in another prosthetic joint. Murray [1] described for the first time the risk of metachronous infections in multiple joints due to hematogenous spread. Studies by Parvizi et al. [2] and Leung et al. [3] both demonstrated that the majority of recurrent infections following PJI due to methicillin-resistant *Staphylococcus aureus* (MRSA) were reinfected with the same organism (66.7 and 89.9%, respectively).

Preexisting PJI was identified as a significant risk factor for a subsequent infection in a study by Luessenhop et al. in 1996 [4]. The presence of rheumatoid arthritis and a prior sepsis were shown to be significantly associated with a higher risk for development of subsequent PJI ($p < 0.001$ and $p < 0.0001$, respectively).

Another study by Jafari et al. [5] retrospectively identified 55 patients with PJI who had another prosthetic joint in place at the time of presentation. Eleven of them (20%) developed a PJI in a second joint, with the same bacteria in 36% of cases. Zmistowski et al. [6] found that recurrent PJI was due to the same organism as the index infection (PJI persistence) in 31.5% of 92 relapsed cases, following two-stage arthroplasty failure. A new organism (PJI reinfection) was observed in 68.5% of these cases. The only independent predictor of PJI persistence versus new infection was the original infecting organism, specifically Staphylococci (MRSA in particular). Moreover, polymicrobial PJIs were more frequently involved in immunocompromised hosts.

Bedair et al. [7] confirmed these observations in a multicenter, retrospective cohort study with 90 patients previously treated for PJI undergoing a second primary total hip or knee arthroplasty (THA or TKA). The study showed that patients with a history of PJI had a

higher risk of developing PJI in a subsequent THA or TKA (10 of 90, versus 0 of 90 in the control group; risk rato: 21.00; 95% confidence interval (CI), 1.25-353.08; p = 0.04). The authors found that a second PJI occurred more frequently in those whose initial infection was by a staphylococcal species (odds ratio (OR), 4.26 p = 0.04). The infecting organisms were the same species in the first and second PJI in 40% of cases, and all four of these were caused by Staphylococci.

Based on the available data, it appears that patients with a prior PJI who are undergoing elective arthroplasty are at higher risk of subsequent infection. The infecting organism for the second joint is most of the time same as the first infecting organism. Taken together, we feel that antibiotic prophylaxis for patients with a prior PJI who are undergoing an elective primary or revision arthroplasty needs to be altered. These patients may require administration of an alternative or additional antibiotic(s). For example, patients with a prior PJI by a gram-negative organism should receive prophylactic antibiotics against gram-negative bacteria. The same applies to patients with a prior MRSA infection and so on.

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QUESTION 7: Should prophylactic antibiotic therapy be administered for an extended duration in patients admitted to the Intensive Care Unit (ICU)?

RECOMMENDATION: Surgical prophylactic antibiotic therapy should not be administered for an extended duration in patients admitted to the ICU.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

The literature on surgical site infections (SSIs) classifies SSI risk factors into intrinsic (patient) related (e.g., age and underlying morbidity) and extrinsic (procedure) related (procedure, facility, pre-and intraoperative factors), both being either modifiable or not [1]. Admittance to the ICU is not treated as an independent risk factor, although risk factors for SSIs and risk factors for ICU admittance are correlated (age, co-morbidity, complexity of procedure). Using the published search algorithm from the World Health Organization (WHO) guideline's literature review and narrowing it with the term "ICU" and expanding it with the term "observational study," 180 articles were retrieved from October 1, 2015 until present (PubMed 39, Embase 84, Central 57). All abstracts were screened, but none found relevant for the question of extending antibiotic duration in patients admitted to the ICU. Using the unaltered WHO search algorithm (without narrowing with "ICU" and expanding with "observational study"), another 23 PubMed articles not covered within the first search were identified, but none of the screened abstracts were relevant. An unsystematic search in the PubMed Clinical Queries search was then performed with the terms "(Therapy/Broad [filter]) AND (antibiotic prophylaxis extended)" returning 245 articles. All titles were screened and abstracts of putative relevance reviewed and none were found to be relevant. The 34 articles retrieved with a modified search term (Therapy/Broad [filter]) AND (antibiotic prophylaxis prolonged ICU) were not found to be relevant either. Thus, no studies were found examining extended antibiotic prophylaxis in ICU patients when these patients are considered as a separate patient category and there are no data to support or refute an extended duration for preventing SSIs solely based on the admittance to the ICU.

However, ICU patients are included in the core randomized controlled trials (RCTs) showing no benefit of extending antibiotic prophylaxis past wound closure [2,3] albeit not specifically for arthroplasty patients. Since the publication of the Proceedings of the International Consensus Meeting on Periprosthetic Joint Infections in 2013, three major literature reviews and guidelines on prevention of SSI have been published from WHO [2], Centers for Disease Control and Preventiopn (CDC) [3], and the American College of Surgeons and Surgical Infection Society (ACS/SIS) [1], respectively. The CDC and WHO guidelines agree on not extending prophylaxis past wound closure based on a comprehensive systematic literature review, but the strength of the data supporting the recommendation for arthroplasty have been questioned [4–11]. The ACS/SIS makes an exception for prophylactic antibiotics past wound closure for joint arthroplasty, on the grounds that optimal antibiotic therapy for these patients remains unknown, but refers to the American Society of Health-System Pharmacists (ASHP); Infectious Diseases Society of America (IDSA); Surgical Infection Society (SIS); and the Society for Healthcare Epidemiology of America (SHEA) guidelines for a total antibiotic prophylaxis duration ≤ 24 hours [12]. A recently published meta-analysis and review on postoperative antibiotic prophylaxis in knee and hip arthroplasty did not find evidence to show efficacy of extended antibiotic prophylaxis for the prevention of SSI in patients undergoing total hip or knee arthro-

plasty. It did however question the quality of the existing evidence and call for new and sufficiently powered RCTs to settle the issue [12]. None of the guidelines or the extensive literature reviews underpinning them thus makes a distinction or specific recommendation for patients admitted to the ICU in general or for use of extended antibiotic prophylaxis for ICU patients in particular. However, ICU patients are included in the core RCTs forming the basis for the strong recommendations of not extending antibiotic prophylaxis after completion of the operation.

ICUs are heterogeneous and ICU capacity varies greatly across hospitals and countries. Consequently, both patient morbidity and hospital policies for ICU admittance will vary, making studies examining extended antibiotic prophylaxis based on ICU admittance unlikely. Should they be undertaken, their external validity would for the above-mentioned reasons be questionable.

The purpose of prophylactic antibiotic therapy in orthopaedic surgery is to prevent SSIs, for which a narrow-acting antibiotic with gram-positive coverage is a proven and sufficient option [13]. Prevention of remote infections in patients admitted to the ICU would have required a different prophylactic approach, including administration of broad-spectrum antibiotics and selective digestive decontamination (SDD), as opposed to the narrow spectrum antibiotics for SSI prevention. Although there are some data to support such a strategy, mainly from ICUs with low levels of antibiotic resistance [14], it remains highly controversial due to concerns of long- term resistance promotion and disturbance to the gut microbiome [15]. There is currently insufficient evidence to recommend its use in settings with high levels of antibiotic resistance [16]. Though an in-depth discussion of the issue is beyond the scope of the assigned question, the increased sense of urgency regarding resistance prevention following the 2014 WHO report on global resistance [17] speaks strongly against adoption of this strategy.

In addition to high awareness, prompt diagnostic workup and early initiations of broad empiric antibiotic therapy are the core interventions for reducing infection related complications in the ICU [18]. The continuation of a narrow-acting antibiotic therapy from the operating theater into the ICU may give a false sense of security and both obscure and delay these interventions, or even harm patients by promoting antimicrobial-resistant bacteria [19,20].

Arguably, the immunosuppressed state following surgery and trauma could be enhanced in patients ill enough to require treatment in the ICU, thus justifying implementation of antibiotic prophylaxis recommendation for immunosuppressed patients. However, despite not identifying studies addressing extended surgical antimicrobial prophylaxis (SAP) in arthroplasty for immunocompromised patients, the CDC guidelines give a strong recommendation (category 1a) against extended SAP in the immunocompromised patients based on their inclusion in the core RCTs with high quality evidence for SAP ≤ 24 hours postoperatively [21].

In an editorial commenting on a survey of 67 ICUs finding 50% of antibiotic prescriptions being continued beyond 72 hours despite absence of a definitive infectious source [22], the editor states that "there is a pervasive belief that an error of commission" (continuation of empiric antibiotics in the absence of evidence of infection) "is somehow better or safer than an error of omission" (ceasing antibiotic therapy when there is some chance–however slim–that the patient will benefit) [23]. This statement also applies fittingly to the question of extended prophylaxis in patients admitted to ICU; with a real threat of running out of effective antibiotics due to indiscriminate use, extending prophylaxis on the sole ground of ICU admittance should be avoided as there is neither theoretical rationale nor clinical evidence to support the practice.

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QUESTION 8: Does the use of allografts alter the recommended duration of prophylactic antibiotics?

RECOMMENDATION: No. Allografts are avascular materials that are prone to contamination and may serve as a scaffold for bacterial colonization and biofilm production, similar to a prosthesis or osteosynthetic material. However, it is difficult to establish a causal relationship between the use of an allograft and subsequent infection. Thus, there is no evidence to support the use of extended antibiotic prophylaxis.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Allografts are typically utilized to address bone defects or damaged tendons at the time of revision procedures for patients who have already undergone multiple operations. By virtue of their operative history, these patients are already associated with a higher risk of infections (2 to 3 times) [1] compared to primary total joint arthroplasty patients. One recent study of fifty consecutive extensor mechanism allograft reconstructions in total knee arthroplasty (TKA) reported an infection rate of 10% [2]. The pooled infection rate from a systematic review and meta-analysis of proximal femoral allograft in revision total hip arthroplasty (THA) was reported to be 8% [3]. Allografts are avascular materials that, similar to a prosthesis or osteosynthetic material, are prone to contamination and may serve as a scaffold for bacterial colonization and biofilm production. However, it is difficult to establish a causal relationship between the use of an allograft and subsequent infection. The question of whether the antibiotic prophylaxis in such complex cases should be altered is a separate discussion from treating infections arising from undetected contamination of the allograft.

There are no high-quality studies available comparing differences between the duration of systemic antibiotic prophylaxis with and without allograft use in primary or revision total joint arthroplasty. Allograft bone may be utilized in different forms including untreated or processed, gamma-irradiated, chemically sterilized, and as fresh frozen product. A contamination rate of up to 23% immediately after aseptic procurement of unprocessed and unsterilized allograft has been reported [3]. Alternatively, sterilization reduces bacterial contamination rates approaching 0% after multiple decontamination processes [4]. An efficient "prophylaxis" may only be expected after using processed or sterilized allografts [5], perhaps by conferring additional local antimicrobial protection [6].

Two-stage procedures for infected TKA [7] and THA [8] with allograft bone demonstrated no differences with respect to short and long durations of antibiotic therapy and reinfection rates; however, antibiotic-impregnated bone cement was utilized in these cases. Withholding systemic antibiotic therapy has also been reported and recommended following revision (THA) for periprosthetic joint infection with adjunctive local antibiotic bone cement elution, except in cases of multiple-operated patients infected with highly-resistant organisms [9]. High quality studies evaluating the optimal duration of prophylactic antibiotics during allograft reconstructive procedures are warranted.

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1.4. PREVENTION: ANTIMICROBIALS (LOCAL)

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QUESTION 1: Is there sufficient evidence to support the use of antibiotic-loaded cement in primary total knee arthroplasty (TKA) or total hip arthroplasty (THA) to reduce the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: There is no conclusive evidence to demonstrate that routine use of antibiotic-loaded cement in primary TKA or THA reduces the risk of subsequent SSIs/PJIs. Recent high level evidence and registry data has not demonstrated a reduction in SSI/PJIs. Furthermore, the added cost, the potential for the emergence of resistant organisms and the potential adverse effect of antibiotics on the host provide adequate reasons to refrain from routine use of antibiotic loaded cement during primary total joint arthroplasty.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 38%, Disagree: 58%, Abstain: 4% (NO Consensus)

Authors: Yale Fillingham, Ali Parsa, Sergei Oshkukov, A. Seth Greenwald

QUESTION 2: Is there a role for the use of antibiotic-impregnated cement in primary total joint arthroplasty (TJA)?

RECOMMENDATION: Antibiotic-impregnated cement may be used during primary TJA to reduce the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs). The benefits of antibiotic-impregnated cement versus its cost and other potential adverse effects, may be most justified in patients at high risk of infection

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 7%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

The concept of using bone cement as a depot for antibiotics makes sense, as it allows for delivery of antibiotics directly to the site of potential infection. However, its role in the prevention of infection remains controversial [1–3].

The elution profile of cemented antibiotics has been evaluated, which demonstrates the elution kinetics of vancomycin, tobramycin, gentamicin, moxifloxacin and clindamycin are better than cefazolin, daptomycin, meropenem, ertapenem, cefotaxime, ampicillin, amoxicillin-clavulanate and cefepime [4–6]. Thus, the two most common antibiotics mixed with bone cement are vancomycin and aminoglycosides such as tobramycin and gentamicin.

Recent annual arthroplasty registries have shown that 96.3% of total knee arthroplasties (TKAs) and 93.7% of total hip arthroplasties (THAs) using cement, used antibiotic-loaded cement [7]. Plain cement has a slightly higher rate of revision than antibiotic-loaded cement when used in TKA [7]. Likewise, in THA, a lower rate of revision is observed for antibiotic-loaded cement in the first five years from surgery [7]. However, the rates of revision in THA were no different between antibiotic-loaded and plain cement beyond five years [7].

Commercially available antibiotic-loaded cements include Palacos® R+G (Zimmer Biomet), Simplex™ P with Tobramycin (Stryker), Smartset™ GHV (DePuy) or Refobacin® (BioMet), but several concerns remain about having readily available antibiotic-loaded cements. Studies have raised concerns regarding the following: (a) increasing microbial resistant; (b) insufficient dose of antibiotic in commercial preparations; (c) additional unnecessary cost; and (d) reduced mechanical properties of antibiotic-loaded cement [7–10].

While most primary THAs in the United States are done with cementless fixation [11], cemented THA is still commonly used in other geographic regions of the world. In the case of cemented arthroplasty, a retrospective comparison study on the use of antibiotic-loaded cement demonstrated an approximately 50% lower infection rate and lower rate of wound infection [11,12]. In addition to lower rates of infection, there is evidence that the addition of antibiotics to the cement leads to a reduction of all time failures of THA [13,14]. Results of a recent systematic review and meta-analysis on 12 clinical trials showed that conventional ventilation together with systemic antibiotics and antibiotic-loaded cement was most likely to provide the best protection against THA-related SSIs [15].

Previous evidence has shown that antibiotic-loaded cement together with systemic antibiotic prophylaxis was effective in reducing PJI in TKA compared with plain cement and systemic antibiotic prophylaxis [16–18]; however, new evidence does not support these results. Two recent prospective studies showed that antibiotic-loaded cement did not reduce the rate of deep infection following primary TKA compared with plain cement [19,20]. More recently, a systematic review on the use of antibiotic-loaded cement in total joint arthroplasty evaluated six articles encompassing 6,318 arthroplasties. Among the study population, 3,217 of these arthroplasties received antibiotic-loaded cement and 3,101 arthroplasties served as the control. Only two studies showed a significant effect of antibiotic-loaded cement in preventing deep infection in primary TKA. Contra-

dictory results were reported in the remaining four prospective and randomized clinical trial studies that showed no statistical difference between the two groups in terms of the incidence of deep or superficial SSIs [21]. In another meta-analysis, Kleppel et al. reported on 4,092 patients following TKA (3,903 primary TKA and 189 revision TKA). At the average follow-up time of 47.2 months for primary TKA, the use of antibiotic-loaded cement did not have a significant reduction in PJI/SSI [22]. Additionally, an analysis of 64,566 joints from the New Zealand Joint Registry demonstrated that the use of antibiotic-laden cement was actually associated with an increase in revision for PJI after a multivariate analysis (odds ratio (OR) 1.93, 95% confidence intervals (CI) 1.19 to 3.13) [23].

We must also consider the cost associated with the use of the antibiotic-loaded cement. Industrially manufactured antibiotic-loaded bone cement may be preferred, due to the ease of access [24]. However, biomechanical and elution testing has demonstrated 1-gram of vancomycin in handmade antibiotic-loaded cement can reduce the cost without compromising the mechanical strength or elution of the drug [25]. Additionally, vancomycin potentially has a higher antimicrobial activity when compared with gentamicin for methicillin-resistant *Staphylococcus aureus* (MRSA) while remaining heat-stable with adequate elution [26–28].

Overall, the literature still lacks an appropriately sized randomized clinical trial to better support the use of antibiotic-loaded cement.

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QUESTION 3: What is the optimal antibiotic(s) dosage to be used in cement during reimplantation that does not significantly interfere with the mechanical strength of cement used for fixation?

RECOMMENDATION: The mechanical strength of most cement is maintained if ≤5% (w/w) of antibiotics is added (equating to 2 grams in a 40 gram packet).

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Several publications have investigated the mechanical characteristics of bone cement in vitro [1-12]. When reviewing in vitro studies on the mechanical strength of bone cement, one must assume that mechanical fixation strength in bone after a one- or two-stage revision for infection would equate to fixation of bone for a primary joint arthroplasty. The mechanical strength of antibiotic-loaded bone cement (ALBC) depends on the following: antibiotic dose, type of antibiotic, number of antibiotics, time of elution, method of mixing and incorporation of impurities/fat/blood [1-15]. Different types of cement also show a variable response to different doses of antibiotics [1, 4, 6, 9, 14].

Unfortunately, most investigations of one and two-stage exchange for prosthetic joint infections (PJIs) did not include details of antibiotic loading into reimplantation cement or used multiple different antibiotic loading regimens. Ultimately, 24 investigations with a consistent antibiotic loading of bone cement before prosthetic reimplantation during one- or two-stage revision for PJI were identified (Table 1). The collective information regarding the details of antibiotic loading in the reimplantation cement was compiled (Table 2).

Investigations examining the mechanical properties of ALBC are all in vitro investigations. Therefore, the loading conditions at the revision total hip and knee arthroplasty (THA, TKA) in vivo bone-implant interface are 1) poorly understood and 2) not adequately modeled to translate the mechanical behavior of ALBC from in vitro studies to these complex in vivo environments. In general, the addition of up to 2 gm of a single powdered antibiotic per 40 gm pack of polymethyl methacrylate (PMMA) has not been shown to have significant deleterious effects on ALBC mechanical properties [16]. More contemporary investigations quantifying the mechanical properties of dual-antibiotic loaded PMMA demonstrate that up to 3 gm total of powdered antibiotics can be included into a 40gm pack of PMMA before compressive strength is decreased below the International Organization for Standardization (ISO) standard [17].

Investigations in this literature review (Table 1) rarely addressed prosthetic aseptic failure following revision for PJI. Furthermore,

TABLE 1. Summary of literature pertaining to antibiotic-loaded cement

PubMed ID	One-stage vs. Two-stage	# Investigated Prostheses	Follow-up Interval (months)	ALBC Details	% Failure
24923669 [18]	One	28	78	1 gm Gent, 1 gm Vanc per pack	0
7497685 [19]	Two	26	31	1.2 gm Tobra per pack PMMA	0
10535593 [20]	Two	40	40	1.2 gm Tobra per pack	25
10990301 [21]	Two	45	48	1.2 gm Tobra per pack	9
11097443 [22]	Two	69	63	1 gm Tobra per pack	9
11216723 [23]	Two	53	56	1.2 gm Tobra per pack	17
12051001 [24]	Two	10	18	0.5 gm Gent per pack	0
15343539 [25]	Two	24	33	2.4 gm Tobra, 1 gm Vanc per pack	8
15991126 [26]	Two	44	65	1.2 gm Tobra per pack	3
15662313 [27]	Two	50	73	1.2 gm Tobra per pack	4
17162176 [28]	Two	21	52	1 gm Tobra per pack	5
17966006 [29]	Two	24	48	1 gm Gent, 1 gm Clinda per pack	4
19553076 [30]	Two	53	49	750mg cefuroxime	17
19299221 [31]	Two	13	48	2 gm Vanc per pack	0
20087702 [32]	Two	27	58	1 gm Gent, 1 gm Clinda per pack	4
20202852 [33]	Two	10	31	0.5 gm Gent, 1 gm Vanc per pack	0
22863338 [34]	Two	21	32	0.5 gm Gent, 1 gm Vanc per pack	4
26272061 [35]	Two	82	36	0.5 gm Gent per pack	15
21866421 [36]	Two	117	46	1.2 gm tobra,1 gm Vanc per pack	28
14563794 [37]	Two	58	41	0.6 gm Tobra per pack	4
15190550 [38]	One	22	120	1.2 gm Tobra per pack	9
10611868 [39]	One	24	108	2 gm 1st Generation Cephalosporin per pack	8.3
721853 [40]	One & Two	67	24	0.5 gm Gent per pack	12
3769248 [41]	One	100	38	0.5 gm Gent per pack	9

TABLE 2. Summary of pooled data pertaining to antibiotic-loaded cement at reimplantation

Variable	Tobra (T)	Gent (G)	Vanco (V)	Cefuroxime	1st Gen cephalosporin	V+T	V+G	G+Clinda (C)
Number of studies	10	4	1	1	1	2	3	2
Two-stage	9	3*	1	1	-	2	2	2
One-stage	1	2*	-	-	1	-	1	-
Dose per 40 gm PMMA pack	0.6-1.2 gm	0.5 gm	2.0 gm	750mg	2.0 gm	1.0 gm V 1.2-2.4 gm T	1.0 gm V 0.5-1.0 gm G	1.0 gm G 1.0 gm C
Number of prostheses	428	259	13	53	24	141	59	51
Average follow-up (mo)	59	29	48	49	108	40	47	53
PJI recurrence incidence (%): range and average	0-25 8.5	0-15 9	0 0	17 17	8 8	8-28 18**	0-4 1.3	4 4

* Numbers do not add up due to one study containing both one-stage and two-stage procedures
** Average significantly skewed to lower value as one study with 28% PJI recurrence incidence included 117 of the total 141 patients

reports of aseptic prosthetic loosening in the setting of prior revision THA or TKA for PJI must be cautiously interpreted as it may represent PJI recurrence. Therefore, conclusions cannot be drawn regarding the clinical effectiveness of any specific ALBC formulation in the prevention of aseptic THA or TKA loosening following revision for PJI.

At this time, there is no definitive conclusion on what prosthetic reimplantation ALBC formulation provides the best eradication of PJI and/or is most protective against subsequent prosthetic aseptic loosening. Any inferences made as a result of this review must be cautiously adopted into clinical practice due to the multiple confounding variables present in different PJI treatment investigations (e.g., patient characteristics, organism resistance profiles, antibiotic spacer differences, length of antibiotic treatment before and after prosthetic re-implantation, etc.). This review demonstrates that prosthetic reimplantation bone cement can be loaded with a wide range of single or dual antibiotics and provide successful PJI control following one- or two-stage PJI revision surgery in a high percentage of prostheses. However, when only ALBC regimens supported by more than one study and 50 patients are considered, prosthetic re-implantation using ALBC containing either 1 gm vancomycin and 0.5-1 gm gentamicin per 40 gm pack of PMMA or 1 gm clindamycin and 1 gm gentamicin per 40 gm pack of PMMA appear to have the optimal ability to control PJI while not resulting in mechanical compromise of the PMMA.

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1.5. PREVENTION: OPERATING ROOM ENVIRONMENT

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QUESTION 1: Does performing a primary total joint arthroplasty (TJA) after a dirty case (infection or open abdomen) in the same operating room increase the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: The little data on this subject suggests that the risk of PJIs may be higher when an elective arthroplasty follows a contaminated case. The risk may be reduced if terminal cleaning of the operating room can be done after the dirty case. Further studies are necessary to elucidate this connection.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

A comprehensive literature review was performed in order to identify all studies on the effect of infection risks in primary TJA following a contaminated case. Searches for the terms "total joint arthroplasty," "infection risk," and "infected case" with different Boolean operators were performed using the search engines Medline, Embase and Cochrane that were searched through February 2018. Inclusion criteria for our systematic review were all English studies (Level I-IV evidence) that reported on infection risk for primary TJA following a contaminated case. Exclusion criteria were non-English language articles, studies > 10 years old, nonhuman studies, retracted papers, case reports, review papers, studies with less than <10 patients in the sample size, studies without clinical follow-up/infection rates and technique papers without patient data. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) criteria were followed. The initial search resulted in 921 papers. After removal of duplicates and evaluation of titles, 170 titles were evaluated, 24 full text papers were read and 4 studies met full inclusion and exclusion criteria to allow for analysis.

There is limited data in literature specific to infection risk when performing primary TJA after a contaminated case, as the number of studies is limited and the number of TJAs performed after an infected case is also restricted. A systematic review was performed specifically evaluating whether nosocomial pathogens persist on inanimate surfaces, such as pathogens from infected surgical cases remaining on surfaces in the operating room [1]. Almost all pathogens including respiratory and gastrointestinal viruses persisted for days on inanimate surfaces, with many gram-positive, gram-negative and fungal pathogens remaining for months. However, pathogen persistence was disrupted if preventative surface disinfection was performed and this was corroborated in a study of 31,499 TJAs where terminal cleaning was effective at reducing bioburden after an infected case and did not increase the likelihood of infection when a case was performed the next day [2]. On the other hand, this same study also demonstrated that infection risk increased by 2.4 times if a TJA case followed an infected case in the same room on the same operative day. Another study

demonstrated this similar finding, as one patient of 39 TJA patients (2.6%) developed an infection after a contaminated case and the organism *Cutibacterium acnes* was the same as the one isolated from the previous infected case [3]. Of note, the sample size was small in this study, although this study encompassed a 5-year study period, indicating that few TJAs were performed after infected cases. On the other hand, a previous study examining 85 TJAs performed immediately after an infected case demonstrated no difference in deep or superficial infection risk at 12 months when compared to a matched cohort of 354 TJAs that did not follow a contaminated case [4]. The pathogen from the TJA infection that followed a contaminated case was due to a different organism than the pathogen present in the preceding infected case. Further research is needed to determine whether infection risk is increased when a primary TJA is performed after a contaminated surgical case.

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QUESTION 2: Does the use of sterile surgical vests decrease the risk of contamination or incidence of infection following total joint arthroplasty (TJA)?

RECOMMENDATION: The use of sterile surgical vests has no bearing on the incidence of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) following orthopaedic procedures.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 85%, Disagree: 6%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

The optimal choice of gown material, type of surgical attire and method of donning operating room personal protective equipment has long been debated. Despite the current era of evidence-based medicine, surgical clothing remains steeped in historic practices based on literature over 30 years old and the notion of "what we have always done." Overall, the evidence surrounding surgical gowning/vests is poor. On systematic review, using PubMed, Ovid-MEDLINE®, Embase, PEDro, Cochrane Library, Scopus, Web of Science, ERIC and CINAHL Plus, we identified 1,356 articles using search terms related to surgical vests, gowns or suits; orthopaedic vests, gowns, suits, exhaust, helmet and surgical textiles. Of these, only 25 were pertinent to our study and represented a heterogeneous group.

It is an issue of significant socioeconomic value given the risk of exposure to contaminants and SSI following TJA. Guidelines from various bodies (World Health Organization, Association of Perioperative Registered Nurses, National Institute for Health and Care Excellence) appear to be based more in "expert opinion" and pragmatic approach rather than scientific evidence. On occasion, these guidelines appear contradictory and incomplete [1,2]. Many papers had major methodological flaws in study design and severe observer bias such that they would not merit inclusion in the study. Of those studies included, several use unproven links such as the reduction of bacterial counts and skin squamous cells as a proxy for infection.

The part of the surgical gown below the level of the operating table and above the chest level appears to be more contaminated [3]. Gowning and gloving appear to generate air particles in an operating room environment, although this appears less so at the level of the operating table under laminar airflow [4].

Exhaust suits have been thought to contribute to reduction of SSI for many years [5]. In addition, it is advocated that they protect the surgical team from contamination during orthopaedic procedures [6]. In a randomly allocated study of different surgical attires used for total knee arthroplasty, body exhaust suits produced less air contamination than occlusive polyester gowns, but no difference was identified in wound contamination [7]. In a combination of hip and knee arthroplasty series, filtered exhaust helmets provided no increased protection against bacterial contamination in the area of the surgical field versus conventional hoods and masks [8]. In comparison to established occlusive polyester gowns, more modern liquid-proof fabric gowns have received criticism that they produce increased air contamination [9]. Disposable non-sterile hoods appear to be equally efficient to helmet systems in containing bacteria in air and surgical site surface [10]. In another study, space suits appear to cause more particle counts in the operating room with surgeon motion compared to standard surgical gowns [11]. Space suits do seem to offer protection in bacterial air contamination at the surgical site compared to conventional surgical suits [12]. Disposable polypropylene clean air suits with cuffs at the sleeves and legs appear to reduce air contamination compared to other suits [13,14]. Reusable surgical gowns show more bacterial penetration compared to disposable spun-bonded gowns [15,16]. Tightly woven special scrub suits do not seem to reduce air or wound contamination with methicillin-resistant *Staphylococcus epidermidis* (MRSE) and the most common source of MRSE remains the patient [17].

Modern positive-pressure surgical helmet systems differ from the earlier negative-pressure body exhaust systems, which were noted to reduce surgical site infection [18]. Furthermore, not all surgical helmet systems compare similarly as far as the contamination of the glove-gown interface is concerned. Specifically, positive pressure systems show more contamination in this area, even compared to conventional sterile gowns [19]. This has been attributed to contamination at the glove-gown interface [20,21]. A randomized study of standard surgical gowns and positive-pressure surgical helmet systems, with and without cuff/glove taping, found

more positive surgical site cultures with helmets and tape, but this was not statistically significant [22]. Direct contact with the sterile helmet is discouraged as a significant number may be contaminated during joint arthroplasty and sterility should not be presumed [11]. In a very large cohort of primary total hip arthroplasty, procedures where a body exhaust system was used showed a higher deep infection incidence, but this did not prove to be a risk factor in multivariate analysis [23].

Overall, the study quality on the subject of sterile surgical attire is low in most instances. Tangible conclusions on which type of attire, material, system and combinations leads to reduction of contamination or incidence of infection following TJA cannot be reached. There appear to be several reports of contamination using sterile helmet systems. Whether that leads to increased incidence of infection remains to be shown. In summary, a weak recommendation of sterile surgical gowns for TJA is put forward, as best "common sense" practice in the absence of robust evidence [24], but the use of modern helmet systems would not be recommended in preventing SSI.

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QUESTION 3: Does the use of personal protection suits (space suits) influence the rate of surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing joint arthroplasty?

RECOMMENDATION: In the absence of strong evidence, we believe the use of personal protection suits does not reduce the rate of subsequent SSIs/PJIs in patients undergoing joint arthroplasty.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 87%, Disagree: 11%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Initial personal protection suits, which aimed to protect the surgical site by reducing microbial contamination and subsequent infection from the operation staff, were negative pressure body exhaust suits with inflow and outflow tubing creating a negative pressure inside the suit. Shed particles were vented away from the surgical site by the tubing. Due to the cumbersome nature of the tubing, more port-

able surgical helmet systems were developed. These helmet systems typically have an intake fan on the helmet, allowing the air to flow across the person's head and neck, and are exhausted by openings in the gown, usually through the lower portion of the gown or other potential openings.

A systematic review of helmet systems and body exhaust suits was published in 2016 [1]. Helmet systems or body exhaust suits were compared to conventional gowns for outcomes of (i) air contamination, (ii) wound contamination and (iii) deep infection. Sixteen articles met inclusion criteria for the various outcomes.

Air contamination: Four studies compared helmet systems to conventional gowns [2–5]. One study [4] reported reduced air contamination; the other three showed no difference [2,4,5]. Five [6–10] of seven studies comparing body exhaust suits showed reduced air contamination. Two studies showed no difference in air contamination compared to conventional gowns [11].

Wound contamination: A single study showed no statistical difference in wound contamination comparing helmet system to conventional gowns [4]. Two of four body exhaust suit comparison studies found a significant advantage to body exhaust suits with less wound contamination compared to conventional gowns [12,13]. The other two studies trended in favor of body exhaust suits [6,7].

Deep infection: Three registry data studies, reporting on four series of patients (two series of total hip arthroplasty (THA) and two series of total knee arthroplasty (TKA) patients), totaling just over 175,000 patients, compared helmet systems to conventional gowns and used reoperation for infection at 6 months [14] or one year as the outcome [15,16]. Hooper reported a statistically higher rate of reoperation for infection within the first six months when helmet systems were used: THA - 0.19% with helmet system vs. 0.06% conventional gown, $p < 0.0001$, and TKA - 0.24% with helmet system vs. 0.098% conventional, $p < 0.001$ [7]. Namba et al. showed no difference in reoperations for infection at one year when a multivariate analysis was used for both THA and TKA [8,9]. Pooled data from these four series showed a non-statistically significant ($p = 0.09$) increase in deep infections (risk ratio (RR) 1.67, 95% confidence interval (CI) 0.92, 3.05) [17].

In contrast, the four studies involving 3,990 patients comparing body exhaust suits to conventional gowns showed a decrease in deep infection when body exhaust suits were used [6–8,13]. The deep infection rate at mean 2.5 years follow-up was 0.17% (3 of 1,795) in the body exhaust group and 1.0% (16 of 1,604) in the conventional clothing group ($p < 0.01$). When data from the above studies was combined in a fixed meta-analysis model, body exhaust suits were associated with a significant reduction in deep infection rates (RR 0.11, 95% CI 0.09-0.46).

Following the publication of the helmet system systemic review, two additional New Zealand Joint Registry data studies have further analyzed the impact of surgical helmet systems on reoperation for infection at 6 and 12 months [18,19]. Multivariate analysis showed no statistical increase (or decrease) in reoperation for infection when surgical helmet systems were used for both primary hip and knee arthroplasty. In the primary knee study there was a non-statistically significant trend ($p = 0.052$) towards reoperation for infection at six months when surgical helmet systems were used (odds ratio (OR) 1.53, 95% CI 1.00 to 2.34) [18]. One additional study, comparing a helmet system to a conventional gown in a simulated surgical environment enclosure, used particle and microbiological emissions as the outcome. Particle counts were statistically higher, while microbiological emissions trended (but not significantly) higher in the helmet system experiments [17].

It is important to note that the type of helmet systems and gowns used were not reported in the above studies on deep infection. Helmet systems vary with respect to the fan type, fan speed, location of exhaust from the gown and material of the gown/toga used with the helmet system. These variables may also influence the potential for contamination. In a study by Fraser et al. one helmet/toga system showed significantly higher rates of contamination at the gown-glove interface relative to other helmet systems and a conventional gown [3]. The other helmet systems in that study showed no statistically increased rate of contamination compared to a conventional gown. The helmet system with the higher risk of contamination at the gown-glove interface used a toga with sleeves made of a stiffer, plasticized material that likely allowed for greater egress of particles at the gown-glove interface.

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QUESTION 4: Does changing the drapes during debridement, antibiotics and implant retention (DAIR) affect the rate of success?

RECOMMENDATION: The impact and effectiveness of changing the drapes during DAIR has not been investigated and therefore it can be performed at the surgeon's discretion.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 94%, Disagree: 5%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

DAIR is a viable and effective option for the management of acute periprosthetic joint infections (PJIs) [1,2]. Published success rates for patients responding to DAIR treatment range from 14 to 100% [3,4]. However, as stated by Tsang et al., published rates improved after 2004 with a pooled mean proportion of success of about 72% [3]. The reason for improvement of success of DAIR is certainly multifactorial and includes a better understanding of the importance of performing a thorough debridement. Numerous factors that influence the outcome of DAIR have been identified including the timing of surgery, the number of procedures, the responsible microorganism, the duration of antibiotic treatment, the exchange of removable components and other factors [3,5–9].

In a review article on DAIR treatment, the only statistically significant determinants of outcome were an early timing of debridement (with a median of < 7 days from the onset of symptoms of infection) and the exchange of removable components [3].

Even though some papers consider the question [10], there are no studies that assess the impact of changing the drapes during DAIR. After a systematic review of 51 papers, only one study was identified that mentioned the use of clean draping during the surgical procedure [11]. Other studies on one-stage exchange after PJI also mention redraping after implant removal and completion of debridement [12].

Changing the drapes during DAIR can be performed at the surgeon's discretion. Further studies are needed to investigate their role and effectiveness in the treatment of early PJI.

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QUESTION 5: Does the use of separate instruments for each side reduce the rate of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) in patients undergoing simultaneous bilateral total hip or knee arthroplasties (BTHA or BTKA)?

RECOMMENDATION: No. The use of separate instruments for each side does not appear to reduce the rate of subsequent SSIs/PJIs in patients undergoing simultaneous BTHA or BTKA.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 72%, Disagree: 19%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

The proportion of one-stage bilateral total joint arthroplasty (BTJA) to unilateral total joint arthroplasty is increasing in the United States. This trend may be driven by the epidemic of obesity and its contribution in the progression of osteoarthritis and the expansion of total joint arthroplasty (TJA) to younger, healthier and more active patients [1–3]. All of these factors result in a higher demand for the procedure. Advances in anesthesia, surgical technique and perioperative care may further contribute to the increase of one-stage BTJA [4].

One-stage BTJA is a relatively safe procedure, especially following appropriate patient selection [5,6]. The benefits of one-stage BTHA include a single anesthesia and single hospital stay, resulting in cost reduction [7] and shorter overall hospital length of stay (LOS) [8,9]. Some studies advocate BTHA as they have demonstrated that rates of perioperative complications are similar between one-stage BTHA and unilateral total hip arthroplasty (THA) [10,11]. On the other hand, opposing studies have found that one-stage BTHA poses greater risks to patients, including increased transfusions, greater adverse events and suboptimal functional outcomes [12–15]. Most studies focus on mortality, pulmonary embolism (PE), deep venous thrombosis (DVT) and cardiovascular complications, but data on SSIs or PJIs is limited in the literature.

SSI/PJI is a significant problem and is associated with increased morbidity, mortality and medical expenditures [16–22]. Increased surgical duration, blood loss and need for allogeneic blood transfusion are risk factors for SSI/PJI [23,24]. The literature is divided with respect to wound infection rates following one-stage BTKA and unilateral total knee arthroplasty (TKA). Authors who have observed a higher infection rate in one-stage BTKA surgery blame the longer operative times, increased number of medical personnel in the operating room and a lack of rescrubbing, redraping and instrument changes for the second arthroplasty [25]. Others have reported rates of SSIs after one-stage BTKA and BTHA to be no higher than those following procedures performed unilaterally or staged. This may be due, in part, to the younger, healthier patient population selected for these procedures [26,27].

A potential source of SSI unique to one-stage BTJA is the use of the same set of instruments in both joints. The procedures may be completed using one or two surgical teams, as well as one or two sets of instruments. Reduced SSI/PJI following BTJAs using separate instruments for each side has not been demonstrated. There is currently limited and inconclusive evidence in the literature [28–31].

In 2006, Gonzalez Della Valle et al. [28] considered the hypothesis that the prevalence of early deep infection would be lower on the second side when a completely new set of sterile instruments was used for the second side. The authors retrospectively reviewed the prevalence of deep infection in 271 consecutive cases using two different sterile setups (group 1) and 289 cases using the same setup (group 2). In group 1, there was one deep infection affecting the first side, while there were no deep infections in group 2. In group 2, one patient developed a superficial infection on the second side requiring readmission and intravenous antibiotics. Given the very low prevalence of deep infection of the first and second side (0.2% and 0%, respectively), the study was underpowered to detect a difference – 2,300 patients would be needed in each group to achieve statistical significance. The results of this study should be considered with caution, as they are the result of experienced surgical teams specialized in hip arthroplasty surgery, operating in laminar flow rooms, and using body exhaust suits. Without these conditions, the rate of infection in single-stage bilateral hip arthroplasties performed with the same set of instruments may be higher. Based on this experience, the use of the same set of instruments for the second side in the operating conditions described in this study appears to be safe [28].

The remaining three studies compared outcomes of bilateral to unilateral TKAs. Two of the three studies used separate instrument sets in the bilateral procedures and observed infection rates of 0% in 227 patients [29] and 2.7% in 92 patients [30]. The final study used the same set of instruments in the bilateral procedures and observed an infection rate of 3.5% in 72 patients, attributing possible sources of infection to prolonged operation time, increased number of assistants in the operating room, not redraping and rescrubbing and not changing instruments [31]. The latter conflicts with the conclusion reached by Gonzalez Della Valle et al. which posited that use of the same instruments is considered safe [28]. Three of the four studies found one-stage BTJA to be generally safe [28–30], with the exception of Luscombe et al. [31] who concluded that staged bilateral procedures may be safer.

There is currently not enough clinical evidence to show that the use of separate instruments for each side during simultaneous BTJA reduces the rate of subsequent SSI/PJI. While the retrospective study from Gonzalez Della Valle et al. did find no difference in infection rates between same and separate instrument procedures, its retrospective nature and lack of statistical power are not strong enough to reach a clinical conclusion regarding standard of practice for using one or two instruments sets. The use of one instrument set does appear to be safe with the available evidence.

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QUESTION 6: Does routine use of a new set of surgical instruments and equipment following debridement and before reimplantation reduce the risk of surgical site infections/periprosthetic joint infections (SSIs/PJIs) recurrences? Is it necessary to change all surgical fields before the final reimplantation in septic revision surgery?

RECOMMENDATION: The change of the surgical field following debridement of an infected joint leads to a reduction in the bioburden and stands to improve outcome of surgical intervention and should be considered.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

There are no specific studies that have addressed the levels of contamination of instruments in infected revision surgeries. Different studies have addressed surgical instrument contamination in orthopaedics and other specialties with no definite recommendations. Some have shown a level of surgical instrument contamination in contaminated and infected operations, implying the instruments will be contaminated by the surgery itself [1,2]. Furthermore, studies have shown that instruments also become contaminated during what are considered to be clean procedures [3].

Pinto et al. showed that in clean orthopaedic surgeries, 47% of the instruments were contaminated. In the same study, an even higher rate of 70% had positive cultures in contaminated surgeries and up to 80% in infected cases [4]. They concluded that there was a significant difference in microbial growth between the clean and contaminated surgeries and between the clean and infected surgeries. In a different study, Evangelista dos Santos et al. evaluated patients undergoing gastrointestinal surgery and found that the surgical wound classification significantly affected the microbial load recovered on instruments [5]. Microbial loads were higher on instruments used for contaminated procedures.

Not all studies share the same results. There is a contradictory report from Nystrom which found that regardless of the classification of orthopaedic operations as clean, contaminated or infected, similar contamination rates were observed in splash basins (75%, 80% and 71% respectively) [6]. They concluded that the data did demonstrate a relatively higher correlation between splash basin contamination and contaminated and infected cases but this was not significant.

When evaluating correlation between contaminated instruments and infection risk, only one study was identified. Dancera et al. showed post sterilization contamination of surgical instruments was linked with an increased rate of deep SSIs in orthopaedic and ophthalmological patients [2]. This seems to link contamination of surgical instruments to increased risk of infection.

In joint arthroplasty surgery literature, Davis et al. showed that in 100 consecutive primary hip and knee arthroplasty operations under laminar flow, instruments get contaminated. 11.4% of suction tips, 14.5% of light handles, 9.4% of skin blades and 3.2% of deep blades were seen to have positive cultures [7]. In conclusion, 63% of operations showed contamination in the field of operation. In a different study evaluating electrocautery tips, Shahi et al. found in 100 consecutive primary total hip arthroplasties (THAs) and aseptic revision THAs that up to 6% of tips were contaminated [3]. None of these patients continued to have a PJI/SSI. Robinson et al. also found that 41% of suction tips had evidence of bacterial colonization in THA surgery undertaken in ultraclean air operating rooms [8]. Furthermore, few studies have focused on elements of the surgical field other than the instruments. Beldame et al. found a surgical

glove perforation rate of 3.5% and glove contamination rate of 6% during total hip reduction (THR) and an overall glove contamination rate of 3.38% in elective THA [9].

Literature suggests that instrument contamination even occurs during primary and clean arthroplasty surgery. This contamination does not seem to translate into an increased risk of SSI/PJI. Although some studies do show that contamination is higher in contaminated and infected surgeries, conflicting evidence exists in whether it translates into clinical infection. Non-arthroplasty literature seems to support that contaminated instruments translate to active infection but few low evidence studies have been identified.

We consider that with these findings, although limited evidence is available, especially related to infected arthroplasty surgery, the routine use of a new set of surgical instruments and equipment following debridement and before reimplantation in infected revision arthroplasty surgery should be considered. This could potentially reduce the risk of having contaminated instruments and therefore reduce the risk of contamination overall in the surgical field, potentially reducing the risk of SSI/PJI.

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QUESTION 7: Is there a concern for contamination of the surgical field by particles, such as cement, that may escape the wound intraoperatively by coming into contact with the ceiling light or facial masks and fall back into the wound?

RECOMMENDATION: There is logically a high risk that particles which fall into the wound after coming into contact with unsterile equipment (e.g., ceiling lights, facial masks) will contaminate the surgical field. However, no studies investigating this hypothesis directly exist in the current literature. We recommend that surgeons must be conscious of, and take precautions, in order to prevent particles from falling into the surgical field, and should such a scenario arise, to use copious antiseptic solutions, such as dilute betadine, in order to irrigate the wound.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Several studies have shown that high-speed cutters in primary hip arthroplasty and spinal surgery can produce aerosols [1–3]. These aerosols, possibly contaminated with bacterial, fungal or viral agents, are spread over the operating room (OR) and contaminate the environment and all personnel present during the surgical procedure. In revision hip or knee arthroplasty, different tools and high-speed cutters are used for removal of cement from the bony cavities. Some of these tools, particularly ultrasound devices, can vibrate at a high frequency leading to a dissemination of cement particles throughout the operating room [4,5]. In some instances, other instruments such as chisels and osteotomes, used for cement extraction, can propel particles into the ceiling, OR lights or body parts of surgeons or assistants participating in the surgery. The particles that come in contact with an unsterile surface such as the ceiling, facial mask or lights, have the potential to fall back into the wound thereby acting as a vehicle for the transport of infectious organisms into this sterile area.

There are no studies in the literature evaluating the effect of debris that come in contact with an unsterile surface and fall back into the wound. Any assumptions must therefore be based on literature highlighting the role of airborne particles in the OR and their correlation with the risk of surgical site injection/periprosthesic joint infection (SSI/PJI). Airborne particles are a source of bacterial inoculation of the wound and can result in postoperative SSI/PJI [6–8]. Therefore, significant efforts are made to reduce the airborne particulate load. Studies suggest that particles larger than 10µm are large enough to carry viable bacteria [9]. Furthermore, as studies suggest that air turbulence and shedding of bacteria by OR traffic can result in an increase in bacterial counts in the sterile fields [10–12], it may be plausible to assume that larger debris may cause similar disruptions in airflow and increase the bioburden. Additionally, existing literature suggests that splash basins used in the OR are often contaminated with bacteria [13,14]. Non-sterile wound debris falling into such basins may be contributing to their contamination, but no study has demonstrated this theoretical possibility.

In summary, despite the absence of any specific studies demonstrating a contamination risk of the sterile operating field from "splash-back" of wound debris, we recommend that surgeons make every effort to mitigate this problem. Rachha et al. reported a technique for cement extraction that will likely prevent this problem. This was a transparent pulsed lavage shield made with plastic material that does not hinder the dexterity or vision of the surgeon. Non-

sterile objects, such as the OR lights, should be kept as far away from the surgical field and sterile equipment as practically possible. It is plausible that contaminated particles may fall into the surgical field during orthopaedic procedures, if such scenario arises, we recommend that copious irrigation of the operative field with the use of normal saline and antiseptic solutions, such as dilute betadine, be performed.

Further basic science (simulation-based) and implementation research in this area is warranted.

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1.6. PREVENTION: SURGICAL TECHNIQUE

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QUESTION 1: Does the use of a tourniquet influence the rates of surgical site infections/periprosthetic joint infections (SSIs/PJIs) in primary or revision total knee arthroplasty (TKA)?

RECOMMENDATION: The literature is inconclusive regarding the use of a tourniquet during TKA and its potential to increase the risks for SSIs/PJIs in TKAs. Tourniquet times and pressures should be minimized to reduce this risk.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

The use of a pneumatic tourniquet during TKA has long been a standard for this procedure. However, concerns have arisen over the ischemic injury that can occur from tourniquet use. This has prompted many authors to conduct studies evaluating the use and non-use of a tourniquet and its effect on perioperative blood loss, postoperative pain and function and postoperative complications [1–7]. However, many of these studies are small, randomized controlled trials (RCTs) that lack the power to definitively state the influence om tourniquet use of SSIs and PJIs.

Liu et al. showed in a RCT of 52 patients undergoing simultaneous bilateral TKA that tourniquet use was associated with greater wound ooze and blistering, as well as the only deep infection in the cohort occurring in a TKA case that had been performed while using a tourniquet [8]. In a 31-patient RCT, Clarke et al. demonstrated that increased tourniquet pressures led to sustained wound hypoxia up to one week following surgery [9]. A meta-analysis by Yi et al. evaluated 13 RCTs of tourniquet use comprising 859 patients. Of these 13 studies, 3 evaluated infection risk, SSI and PJI together, and they found that tourniquet use was significantly associated with an increased risk of infection [6]. A meta-analysis by Zhang et al. found a similar pooled result with tourniquet use associated with a greater risk of non-thrombotic complications, infection included [10].

Longer tourniquet times, and by virtue longer surgical times, have been associated with an increased risk for both SSI and PJI [11–13]. Willis-Owen et al. in a series of 3,449 consecutive TKAs found that patients who went on to have a SSI/PJI had significantly longer tourniquet times than noninfected patients [11]. Ricciardi et al. found a similar result in their analysis of perioperative variables affecting 30-day readmission [12]. Na et al. evaluated early release of the tourniquet following cementation of components versus reinflation of the tourniquet after controlling bleeding in 206 patients and found that the increased tourniquet time for patients in the reinflation group did not affect the rate of wound complications, SSI or PJI [14]. However, none of these studies were able to propose a cutoff for tourniquet time over which the risk of SSI and PJI begins to increase. These studies also did not differentiate between operative time and tourniquet time. As increased surgical time is a known risk factor for

SSI and PJI, the confounding effect of increased surgical time may be influencing the relationship between tourniquet time and postoperative infections.

There is still much debate over the efficacy of tourniquet use to decrease perioperative blood loss. Ledin et al. conducted a RCT on 50 consecutive TKAs on the use of a tourniquet and found no difference in calculated perioperative blood loss [15]. The meta-analysis by Zhang et al. found that calculated blood loss was greater without the use of a tourniquet, however this did not result in a greater transfusion requirement [10]. Conversely, a meta-analysis by Jiang et al. found that tourniquet use did decrease transfusion requirement in the pooled analysis of 1,450 knees [16]. As allogeneic blood transfusion is a known risk factor for SSI and PJI, limiting blood loss is an important aspect of infection prevention [17–20].

Another concern with the use of a tourniquet during TKA is whether appropriate antibiotic prophylaxis is administered to the surgical site. Friedman et al. evaluated soft tissue and bone concentrations of antibiotics given one minute, two minutes and five minutes prior to tourniquet inflation and found the highest concentrations to be when antibiotics were administered five minutes prior to inflation [21]. Yamada et al. found that when cefazolin was administered 15 minutes prior to inflation, the concentration in bone and soft tissue at the surgical site were above the minimum inhibitory concentration (MIC90) for methicillin sensitive *Staphylococcus aureus*, but below the MIC90 for cephazolin resistant coagulase negative staphylococcal species [22]. Young et al. found that by administering antibiotic prophylaxis intraosseously, higher regional antibiotic concentrations could be achieved, however the clinical efficacy of this in reducing the rates of SSI and PJI still need to be evaluated [23].

The effect that the use of a tourniquet has on the incidence of SSIs and PJIs following TKA has not been fully evaluated. The RCTs of this subject have been of small cohorts of patients that lack the power to evaluate these complications. The meta-analyses on this topic also have not been able to definitively comment, as many studies did not report the incidence of SSI and PJI in their cohorts. Moving forward, studies evaluating the use of a tourniquet during TKA should consider SSI and PJI as a secondary endpoint so that future pooled analyses may be better able to elucidate a connection, if one exists.

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QUESTION 2: Does the surgical approach (parapatellar vs. subvastus) during primary total knee arthroplasty (TKA) affect the incidence of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: The incidence of SSIs/PJIs after primary TKA is not influenced by the surgical approach (parapatellar vs. subvastus).

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

The medial parapatellar approach and the subvastus approach are the most common approach techniques for primary TKA [1]. To date, the question of the best surgical approach for primary TKA is still a matter of debate [2]. Despite the vast body of literature investigating the clinical outcome of patients undergoing TKA with either the medial parapatellar or the subvastus approach, only a limited number of studies focus on their infection rates.

There have been four meta-analyses published to date that compare the subvastus to the medial parapatellar approach as well as one meta-analysis that compares subvastus to quadriceps-sparing approach, which are included in the following references below [1,3–6]. Regarding infection risk, none of these five meta-analyses found a difference.

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QUESTION 3: Does the surgical approach of primary total hip arthroplasty (THA) affect the incidence of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: The surgical approach in primary THA does not affect the incidence of subsequent SSIs/PJIs.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 88%, Disagree: 10%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Many approaches to expose the hip joint have been described. Surgical approaches for THA have evolved to include a minimally invasive posterior approach to minimize soft tissue damage, a resurgence of the direct lateral approach to address concerns of instability and the increased popularity of direct anterior surgery to improve postoperative recovery. Smaller skin incisions combined with less soft tissue damage and improved pain management techniques have resulted in faster recovery times, quicker rehabilitation and shorter hospital admissions. However, the impact of these approaches on the risk of infection has not been studied extensively. We report data from randomized control trials (RCT) and large registry data bases to support our conclusions.

In the English literature, 37 RCTs were found comparing functional and other postoperative results using different surgical approaches for primary THA. None of these, however, was designed to study PJI as the primary outcome. Fortunately, PJI is frequently reported as a secondary outcome. More than half of the RCTs identified (20/37) compared a conventional approach to a minimally invasive approach ("mini"), 12 studied two conventional approaches and 5 evaluated two mini-approaches. The posterolateral (PL) approach in both its standard or minimally invasive iterations were the most frequently examined (22). The primary outcome in the majority (30/36) of these RCTs was the functional assessment of the patients. The sample size of RCTs ranged from 20 to 219 THAs.

In the RCT with the greatest reported sample size, Ogonda et al. [1] followed 219 patients operated through either a standard or minimally invasive PL approach for six weeks. No infections were observed in the standard posterior approach (PA) group, while one deep and one superficial infection were found in the minimally invasive surgery (MIS) group. In another report, Xie et al. [2] studied 92 patients with unilateral primary osteoarthritis who were randomized to undergo a THA using either a supercapsular, percutaneously assisted approach or a conventional PL approach. An intention-to-treat analysis was used, but no infection was noticed in either group. Kim et al. [3] reported one infection in a study in which a mini-posterior approach was compared to a standard PL group. Goosen et al. [4], in a RCT of 120 THAs, described one infection in the "classic" group and no infections in their "MIS" group. Due to the low incidence of PJI, these trials did not have the statistical power to evaluate the relationship between surgical approach and SSI/PJI.

Eight meta-analyses [5–12] of these RCTs have been conducted to compare postoperative results of primary THA when using different surgical approaches: three compared "mini" approaches to standard ones [8,10,11], one compared mini vs. standard PL [7], one compared a direct lateral (DL) vs. the direct anterior approach (DA) [9], two compared PL vs. DA [5,6], and one compared DA, PL, lateral approaches (including the Watson Jones and modified Hardinge approaches), and two incision surgeries [12]. Two of these eight meta-analyses [6–11] were designed to specifically report significant differences in the complication rates between surgical approaches. Putananon et al. [12] performed a network meta-analysis of 14 RCTs (1,017 patients) comparing DA, PL, latera, and two incision [12] approaches and concluded that PL had the lowest risk ratio for overall complications including infection. The systematic review and meta-analysis of Miller et al. [5] was designed to compare postoperative complications of prospective and retro-

spective studies between DA and PL. A total of 7 out of the 19 studies included reported results on infection; six of them were comparative studies and one was a registry paper. PJI rate was reported as 0.2 events per 100 person-years for DA and 0.4 events for PL; this difference was statistically significant (risk ratio (RR) = 0.55, p = 0.002). However, when only the comparative studies were included in the analysis, this difference ceased to be significant (RR = 0.65, 95% confidence interval (CI) 0.16 to 2.7).

Registry data has been published that specifically looked at risk factors for revision and included surgical approach and its impact on infection risk. Due to the size of the data sets involved, registries can adjust the results to account for the impact of variables such as obesity, diabetes and hospital volume on outcomes. Recently, Smith et al. [13] retrospectively evaluated 91,585 THAs from the New Zealand Registry to identify factors that affected the infection rate following THA. Multivariate analysis revealed that the anterolateral (AL) approach significantly increased the PJI revision rate at twelve months when compared to the PL approach (odds ratio (OR) = 1.61, p = 0.005). In another study, Mjaaland et al. [14], analyzing 21,860 THAs from the Norwegian Registry, showed a significant increase in the risk of revision due to PJI when the DL approach was used, compared to DA and AL approaches (RR = 0.53), and the PL approach (RR = 0.57). However, a study [15] from the Swedish Registry showed no difference on infection rate of 90,662 THAs using either PL or AL approach, but it should be noted that no adjustment was made for obesity, Diabetes Mellitis (DM) or American Society of Anesthesiology (ASA) score. In agreement with the Swedish data is a study by Namba et al. [16] which looked at 30,491 THAs in the Kaiser Permanente Registry and did not find an association between SSI and surgical approach when adjusting for a large number of covariates such as the use of antibiotic cement, surgeon volume, age, diabetes, Body Mass Index (BMI), ASA score, and a number of other factors. However, the Kaiser Registry was composed predominantly of patients undergoing PL THA and may not have the data to comment the other approaches. Christensen et al. [17] compared 1,288 PL THAs to 505 DA patients recorded in a private registry and found a much higher incidence of wound complications that required reoperation in the DA group (1.4% vs. 0.2%, p = 0.007), but the incidence of SSI (2 in DA and 1 in PA) and PJI (1 in each group) were comparable.

Lastly, we note that obesity (a risk factor for both SSI and PJI after THA [13,16] may impact the relative risk of any specific surgical approach on infection. Watts et al. [18] stated that obesity is a stronger risk factor when the DA is used. Dowsey et al. [19], reviewed over 1,000 patients undergoing PL or DL THA. The infection rate was higher in obese than in non-obese patients when PA was used (2.5% obese and 18% morbidly obese patients), but they found no significant correlation between the DL approach and obesity. Christensen et al. [17] compared 1,288 PA THAs to 505 DA patients and found a much higher incidence of wound complications that required reoperation in the DA group (1.4% vs. 0.2%, p = 0.007), but the incidence of SSI (2 in DA and 1 in PA) and PJI (1 in each group) were comparable.

In conclusion, surgical approach does not affect the risk of SSI/PJI following primary THA. While some data exists indicating the DL and AL approaches may be at an increased risk of SSI/PJI, the data is by no means definitive. Furthermore, much of the existing data is derived from registries, which have been shown to under-report the incidence of infection [20–22]. More granular data is required in order to make a more informed conclusion on this topic.

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QUESTION 4: Does the use of periarticular injections (PAIs) affect the rate of surgical site infections/periprosthetic joint infections (SSIs/PJIs) recurrence in reimplantation?

RECOMMENDATION: Unknown. PAIs are an effective adjunct treatment for pain control following primary total joint arthroplasty (TJA), but their effectiveness and impact on the rates of SSIs/PJIs in the revision setting has not been investigated. The use of PAIs at the time of reimplantation can be performed at the surgeon's discretion.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 91%, Disagree: 5%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Pain management following primary and revision TJA is crucial to facilitate early mobilization, decrease length of stay, decrease opioid consumption and to improve patient satisfaction [1]. It is known that revision TJA cases such as prosthesis reimplantation are more complex and typically require greater dissection than primary TJA, thus postoperative pain control may be more difficult.

PAIs of anesthetic medications are a proven, effective adjunct to multi-modal pain management protocols in the primary TJA setting [1–3]. While the combination of medications injected varies widely amongst randomized controlled trials (RCTs), PAIs have been shown to provide superior pain control versus the use of patient-controlled anesthesia [4] and femoral nerve blocks [5–7], and PAIs are equivalent to the use of a femoral-sciatic nerve block following primary total knee arthroplasty (TKA) [8]. In a systematic review of 13 RCTs of patients undergoing primary total hip arthroplasty (THA), Marques et al. found patients receiving local anesthetic infiltration to have a greater reduction in pain at 24 and 48 hours postoperatively [1]. However, the impact of PAIs on pain management in the revision TJA setting, along with their impact on the rate of SSI/PJI, has not been investigated.

One consideration is whether corticosteroid should be included in the use of a PAI. There is conflicting evidence as to whether inclusion of corticosteroid in a PAI improves pain control [9–12]. Furthermore, there is the theoretical concern of a potentially increased risk of infection with the inclusion of corticosteroid given its immune-modulating properties [13,14]. No studies in the setting of primary arthroplasty have found a significant difference in SSI rates in PAI containing corticosteroid, and it is worth noting that all these studies were powered using pain as a primary outcome [9, 13,15,16]. Thus, these studies were not designed to determine the influence of corticosteroid on an outcome of low incidence such as SSI/PJI, and the risk posed by intraoperative corticosteroid PAI remains theoretical.

Unfortunately, there are no studies that assess the impact of PAIs on the rates of SSIs/PJIs recurrence during TJA reimplantation. As PAIs assist with pain control in the primary setting, it could be presumed that they are effective during TJA reimplantation, yet this has not been proven. The use of PAIs at the time of reimplantation can be performed at the surgeon's discretion, but the addition of corticosteroid should be cautioned as its immuno-modulating risk may outweigh its questionable benefit. Studies investigating the influence of PAI on the incidence of SSI/PJI following primary and revision arthroplasty are needed.

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QUESTION 5: Does simultaneous bilateral hip or knee arthroplasty (SBTHA or SBTKA) increase the risk of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) compared to unilateral or staged bilateral arthroplasty?

RECOMMENDATION: SBTHA or SBTKA does not increase the risks of SSIs/PJIs compared to unilateral or staged bilateral arthroplasty.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 79%, Disagree: 15%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Since Jaffe and Charnley reported the first SBTHA in 1971 [1], and Ritter and Randolph performed the first detailed study of the functional outcome in 1976 [2], there has been ongoing discussion regarding the advantages and disadvantages of simultaneous bilateral procedures in the patients with bilateral arthritis.

In the absence of a randomized and prospective trial with an adequately powered sample to compare the infection rates in simultaneous bilateral joint arthroplasty with staged bilateral total arthroplasty, knowledge regarding infection rates mostly comes from retrospective studies. Many of these studies are biased, by selection bias, misclassification bias and/or follow-up time bias. Studies analyzing large numbers of patients allow for comparisons to be made regarding complications that occur infrequently, such as infection, but the validity of these comparisons is not known [3].

The reviews of the studies that analyze the probabilities of developing periprosthetic joint infection after simultaneous bilateral total arthroplasty have reported contradictory results. There have been three meta-analyses in recent years, in which the outcomes of SBTKA have been compared with staged bilateral total knee arthroplasty (BTKA). Hu et al. [4] and Hussain et al. [5] concluded that the infection rates were similar between the two groups. Other studies did not observe differences in the infection rate between simultaneous and unilateral or staged BTKA [6–15]. On the other hand, Fu et al. [16] in another meta-analysis concluded that SBTKA was associated with a lower infection rate. Similarly, Poultsides et al. [17] published the only study focused on comparing the rate of infection in a long retrospective series of patients undergoing SBTKA, staged BTKA, or unilateral total knee arthroplasty (TKA). They observed that the overall infection rate after SBTKA (0.57%) was lower compared to the staged (1.39%) or unilateral (1,1%) cohorts. The rate of superficial infection was significantly lower in the simultaneous cohort (Simultaneous: 0.28% vs. Staged: 1.04% vs. Unilateral: 0.87%; P = 0.003), but the rate of deep infection was similar among the groups (Simultaneous: 0.32% vs. Staged: 0.35% vs. Unilateral: 0.24%; P = 0.65).

Meehan et al. [18] used a more sophisticated epidemiologic methodology in an attempt to minimize the selection bias inherent in most published studies. They analyzed the California Patient Discharge database to create an intention-to-treat cohort of patients who originally were scheduled to undergo separate-admission staged BKTA. Important findings included that the SBTKA cohort had significantly lower risks of periprosthetic joint infection (odds ratio (OR) = 0.6, 95% confidence interval (CI), 0.5 to 0.7]; unadjusted rate, 8.7 per 1,000 for the SBTKA cohort compared with 16.5 per 1,000 for the separate admission staged BTKA cohort).

In a retrospective study [19], SBTKA, compared to the unilateral, was associated with increased superficial wound infection (6.0 vs. 0.7%; p = 0.003) and deep prosthetic infection (3.5% vs. 0.7 %; p = 0.02). The rationale behind these studies is that the prolonged operative time, an increased blood loss, an increased number of assistants in the operating room, changing instruments during BTKA and bilateral total hip arthroplasty (BTHA) and no redraping or rescrubbing may predispose these patients to a higher rate of infection [20,19]. Della Valle AG et al. [21] did not demonstrate a statistically significant difference in the rate of deep or superficial infections among patients undergoing simultaneous hip arthroplasty using different or the same set of surgical instruments, arguing that the use of the same set of instruments for the second side arthroplasty appeared to be safe.

Shao et al. [22] found in their meta-analysis, four studies that provided data on infectious complications (including deep and superficial infection) and the pooled data showed a statistically higher infection rate in simultaneous versus staged BTHA (OR = 2.17; 95% CI = 1.27 to 3.71; P = 0.004). In the same way, Berend et al. [23] reported a SSI complication rate of 1.8% SBTHA, which was significantly higher than the rate for staged BTHA. However, Della Valle [21] observed a 0.1% infection rate for SBTHA using the same lateral decubitus position. Other studies comparing SBTHA and unilateral total hip arthroplasty (THA) did not find increased rates of SSI [24–26]. There is only one [27] prospective, randomized, controlled study in literature comparing simultaneous bilateral and staged hip arthroplasties, and no significant difference was found in the incidence of infection between the two hip arthroplasty groups.

It is well known that simultaneous bilateral total joint arthroplasty (SBTJA) is associated with increased blood loss and need for allogeneic blood transfusion compared to unilateral or staged bilateral arthroplasty [8,23–25,27–36]. Pulido et al. [37] found, after multivariable logistic regression analysis in a retrospective study, that with simultaneous bilateral surgery (compared with unilateral procedures) the transfusion of allogenic blood units were independent predictors of PJI after primary joint arthroplasty. Nevertheless, there is contradictory evidence in the different studies on the relationship between allogeneic transfusions and the risk of PJI [38–41].

Having evaluated all available published reports, we believe that the incidence of infection following bilateral TJA (BTJA) performed under the same anesthesia is not significantly higher than the rate of infection following unilateral or staged BTJA.

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1.7. PREVENTION: PROSTHESIS FACTORS

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QUESTION 1: Are there implant materials that mitigate the risk for surgical site infections/ periprosthetic joint infections (SSIs/PJIs) after total joint arthroplasty (TJA)?

RECOMMENDATION: There are various implant materials that can be utilized to reduce the chance for SSIs/PJIs in patients undergoing TJA.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 49%, Disagree: 30%, Abstain: 21% (NO Consensus)

RATIONALE

The skyrocketing increase in number of joint arthroplasty surgeries and their associated failures have raised serious concerns in the field of medicine. Failures of medical devices due to infections have resulted in an increase in number of revision surgeries, and even fatality. Biomaterial-associated infections are fearsome complications of modern orthopaedic surgery, that often leads to prolonged

patient pain and functional losses. While immense efforts to minimize the risk of these infections have intensified over the last decade [1], orthopaedic SSIs continue to occur in worrisome numbers.

The concept of a "race for the surface" was previously proposed by Gristina [2] and Costerton et al. [3]. They described a situation whereby the ultimate fate of the implant is determined by the competition of host cells and bacterial cells. When bacteria won the race, an infection would result, instead of tissue integration. Gristina also realized that bacterial colonization of the tissue around implants was another possible mechanism of infection [2].

Herein we will review, among others, that bacterial adhesion and subsequent biofilm formation may be prevented by modifying the physicochemical surface properties of biomaterials. We will go beyond the mere aspect of implant surface biofilm formation, though. In fact, there are mainly three schools of thought regarding how to manage SSIs and PJIs. First, making the surface of the implant bacteria unfriendly; the concern about such approach is that it does not deal with infected surrounding tissue. Second, applying coatings on the implant surface that incorporate antibiotics, but coating adhesion and stability are concerns. Third, local biodegradable "implants" releasing antibiotics. We will review the benefits and limitations of each approach first. A general discussion will follow concluding that no method is ideal, but that a combination is probably needed. As is self-evident then, no consensus currently already exists.

1. Coating on the implant surface

In this strategic category the surface of the implant is coated with different materials that can release antimicrobials, including polymers, ceramics or metal oxide films. Some of the materials in this category are already on the market and clinical data are available. We will summarize these concepts first, followed by a description of concepts that are the subject of animal studies.

1.1 Gentamicin-poly (D, L-lactide) polymer coating for tibia nails

This is a fully resorbable poly (D, L-lactide) polymer with incorporated gentamicin sulphate. This material exhibits an initial burst release of 40% gentamicin over first hour and 80% of it released with first 48 hours [4].

Fuchs et al. [5] published a case study on 21 patients (13 men, 8 women) and 19 of them completed the 6-month follow-up. No implant-associated infections were seen and only one superficial wound healing was reported in one patient. Authors concluded that the use of the Unreamed Tibial Nail (UTN) PROtect® intramedullary nail was associated with good clinical, laboratory and radiological outcomes after six months.

Metsemakers et al. [6] reported another prospective case studies with the same gentamicin-poly (D, L-lactide) coating on the Expert Tibia Nail (ETN) PROtect™ on 16 patients. They described the outcome of patients treated between January 2012 and September 2013, using a gentamicin-coated intramedullary tibia nail. Treatment indications included acute, Gustilo grade II-III, open tibia fractures or closed tibia fractures with long-term external fixation prior to intramedullary nailing and complex tibia fracture revision cases with a mean of three prior surgical interventions. Outcome parameters in this study were deep infection and nonunion. Authors concluded that no deep infections occurred after placement of the gentamicin-coated nail in studied patient population.

1.2 Disposable Antibacterial Coating (DAC) hydrogel

DAC hydrogel is composed of hyaluronic acid and polylactic acid. It is supplied as powder and can be mixed with antibiotic solutions to form the hydrogel at the time of surgery. Literature data show that all types of antibiotics incorporated in DAC are released within 96 hours [7].

Malizos et al. [8] published a randomized controlled prospective study. A total of 256 patients in five European orthopaedic centers who were scheduled to receive osteosynthesis for a closed fracture, were randomly assigned to receive antibiotic-loaded DAC or to a control implant without coating. Overall, 253 patients were available with a mean follow-up of 18.1 ± 4.5 months (range 12–30). On average, wound healing, clinical scores, laboratory tests and radiographic findings did not show any significant difference between the two groups. Six SSIs (4.6%) were observed in the control group compared to none in the treated group ($P < 0.03$). No local or systemic side-effects related to the DAC hydrogel product were observed and no detectable interference with bone healing was noted.

In another multicenter, randomized prospective study, a total of 380 patients, scheduled to undergo primary (n = 270) or revision (n = 110) total hip (N = 298) or knee (N = 82) joint arthroplasty with a cementless or a hybrid implant, were randomly assigned in six European orthopaedic centers, to receive an implant either with the antibiotic-loaded DAC coating (treatment group) or without coating (control group) [9]. Overall, 373 patients were available at a mean follow-up of 14.5 ± 5.5 months (range 6 to 24). On average, wound healing, laboratory and radiographic findings showed no significant difference between the two groups. Eleven early SSIs were observed in the control group and only one in the treatment group (6% vs. 0.6%; p = 0.003). No local or systemic side effects related to the DAC hydrogel coating were observed, and no detectable interference with implant osseointegration was noted.

1.3 Silver-coated Modular Universal Tumar and Revision System (MUTARS®) for tumor mega-endoprostheses and knee arthrodesis nails

A silver (Ag) film with a thickness of 10-15 µm was deposited on the surface of MUTARS® mega-endoprostheses. This first layer was further coated with another layer of gold of 0.2 µm thick to ensure sustained release of Ag ions [10]. Hardes et al. [11] reported a prospective case study that consisted of 20 patients with bone tumors of the humerus, femur and tibia that were treated with this type of coating with an average Ag amount of 0.91 gm (range: 0.33–2.89 gm). They found that the Ag-levels in the blood did not exceed 56.4 parts per billion (ppb) and can be considered as non-toxic. Additionally, they were able to exclude significant changes in liver and kidney functions measured by laboratory values. Histopathologic examination of the periprosthetic environment in two patients showed no signs of foreign body granulomas or chronic inflammation, despite distant effective Ag concentrations up to 1,626 ppb directly related to the prosthetic surface. The authors concluded that the Ag-coated megaprosthesis allowed a release of Ag without showing any local or systemic side-effects.

In another study by Hardes et al. [10], 51 patients with sarcoma (proximal femur, n = 22; proximal tibia, n = 29) who underwent placement of a Ag-coated megaprosthesis were assessed prospectively over a 5-year period, along with the treatment administered for infection. The infection rate was compared with the data for 74 patients in whom an uncoated titanium (Ti) megaprosthesis (proximal femur, n = 33; proximal tibia, n = 41) was implanted. They found that the infection rate was substantially reduced from 17.6% in the Ti group to 5.9% in the Ag group. Whereas 38.5% of patients in the Ti group ultimately had to undergo amputation when periprosthetic infection developed, these mutilating surgical procedures were not necessary in the study group. The conclusion of the study is that the use of Ag-coated prostheses reduced the infection rate in the medium term. In addi-

tion, less aggressive treatment of infection was possible in the group with silver-coated prostheses.

1.4 Iodine-coated endoprostheses

This type of film was synthesized by using a povidone-iodine electrolyte that resulted in the formation of an adhesive porous anodic oxide with the antiseptic properties of iodine [12,13]. Shirai et al. [13] published on a study with 222 patients who suffered from postoperative infection or compromised status and were treated using iodine-supported Ti implants. The mean age of the patients was 49.4 years (range 5–85 years). One hundred twenty-seven patients were male and 95 were female. Iodine-supported implants were used to prevent infection in 158 patients who were deemed susceptible to infection. They were also used to treat active infection in 64 patients. The mean follow-up period was 18.4 months (range 3–44 months). Acute infection developed in three tumor cases among the 158 patients on preventive therapy. All three recovered without removal of the implants. Infection was cured in all 64 patients with infection. There were two patients with mechanical implant failure, which was treated by re-implantation. Excellent bone ingrowth and ongrowth were found around all hip and tumor prostheses. One year later, the amount of iodine on external fixation pins remained about 20–30%.

1.5 Thermal-sprayed silver oxide containing hydroxyapatite coating

This type of coating on the implant surface is generally prepared by thermal spraying of a mixture of silver oxide and hydroxyapatite (HA) powder using an acetylene torch. The release rate of silver (Ag) ions from this type of coating is usually high until 24 hours after immersion and decreases thereafter. Within the duration of the test, the amount of Ag ions reached 373 ppb at 168 hours [14]. Normal blood Ag concentrations are considered to be below 10 ppb [15]. Toxic side effects of Ag were described for blood concentration of 300 ppb in the form of argyrosis, leucopenia and liver and kidney damage [14,16–18]. Regarding cytotoxicity by Ag, Yamamoto et al. reported that the half maximal inhibitory concentration (IC_{50}) of Ag ion for murine fibroblasts L929 is ~458.6 ppb; further, using $AgNO_3$ for cytotoxicity test, the IC_{50} for murine osteoblastic cells MC3T3-E1 is ~298.9 ppb [19]. Eto et al. [20] recently published a first clinical study result with this implant coating. They prepared an implant for total hip arthroplasty (THA) that was coated with Ag-HA. In this study, the implant contained Ag at a maximum quantity of 2.9 mg/implant. In this prospective interventional study, THA was performed with this implant in 20 patients. They found that blood Ag levels peaked at two weeks after THA and gradually decreased thereafter. The highest blood Ag level recorded during the postoperative follow-up was 6.0 ng/mL, which was within the normal range. The Harris Hip Scores increased in all cases and activities of daily living improved markedly after THA with Ag-HA coated implants. Implant failure was absent on radiography. No adverse reaction to silver was noted and argyria was not observed in any case. No patients have developed infection after surgery. Authors concluded that Ag-HA coated implants markedly improved patients' activities of daily living without causing any adverse reactions attributable to silver in the human body. Ag-HA is expected to reduce postoperative infections and prevent decreased quality of life in patients undergoing prosthetic arthroplasty, thus leading to more favorable outcomes.

After analysis of all above mentioned clinical studies it can be concluded that more prospective randomized controlled trials that investigate postoperative infection rates of the reviewed coatings vs. uncoated control implants are needed.

Other promising approaches regarding the coating of implant with antimicrobials releasing materials are described next.

1.6 Experimental coatings

Most of the currently-available coated implants capable of releasing antimicrobials exhibit a very high initial burst release and release the majority of the drug during the first 48 hours, followed by a prolonged period of drug release at sub-inhibitory concentrations. There is a need for a coating strategy which can deliver antibiotics above minimum inhibitory concentration (MIC) level for longer duration. In this regard, Ducheyne and colleagues developed sol gel silica coating with incorporated antibiotics (vancomycin, triclosan) which exhibits the release of antibiotics above inhibitory concentration for more than four weeks. In vitro and in vivo studies in rat, rabbit and sheep showed excellent results. The in vitro study demonstrated that thin and resorbable controlled release antibacterial sol-gel films can be applied on Ti-alloy substrates. Using a multilayer process, long-term release can be achieved. The release concentrations are such that they exceed the MIC of vancomycin against *Staphylococcus aureus* [21,22]. The in vivo study with the same coating materials demonstrate that a vancomycin-containing sol-gel film on Ti alloy rods can successfully treat bacterial infections in an animal, osteomyelitis model. Radiologically, while the control side showed extensive bone degradation, including abscesses and an extensive periosteal reaction, rods coated with the vancomycin-containing sol-gel film resulted in minimal signs of infection. Micro-CT analysis confirmed the radiological results, while demonstrating that the vancomycin-containing sol-gel film significantly protected dense bone from resorption and minimized remodeling [23]. Another study by Qu et al. demonstrates that triclosan (2,4,4'-trichloro-2'-hydroxydiphenylether), an antimicrobial agent, can be successfully incorporated into micron-thin sol-gel films deposited on percutaneous pins. The sol-gel films continuously release triclosan in vitro for durations exceeding eight weeks (longest measured time point). When inserting percutaneous pins in distal rabbit tibiae, there were no signs of infection around implants coated with a micron-thin sol-gel/triclosan film. Healing had progressed normally; bone tissue growth was normal and there was no epithelial downgrowth. This result was in contrast with the results in rabbits that received control, uncoated percutaneous pins, in which abundant signs of infection and epithelial downgrowth were observed.

Another existing approach to increase the released amount of antibiotics is to combine different degradable polymers into a multilayer system. It also offers the opportunity to include multiple antibiotics that allow modulation of the release profile per antibiotic [24] and additionally degradable surfaces may be inherently resistant to infection [25]. An alternative method to obtain multilayer systems has been described by Shukla et al. who applied tetra-layers of poly-2-dextran sulfate/vancomycin/dextran sulfate by spray coating [26]. They were able to expand the release time to 100 hours.

A major problem with this strategy is the mechanical stability of the film and its adherence to the implant surface. In most of the cases, the films become damaged during the press fit of the implant. Another problem is to elute enough antibiotics for the long time.

2. Chemical modification of the implant surface

This strategy involves the direct immobilization of antimicrobials on the implant surface through chemical bonding. This approach, also known as "contact killing," works by inhibiting bacteria that come into contact with the surface of the implant. One of the approaches in this category is the immobilization of antibiotics to the implant surface. Current immobilization studies focus mainly on binding of vancomycin, which is considered to be a last

resort in treatment of infections caused by multi-resistant bacterial strains [27]. Since the working mechanism of vancomycin requires penetration of the cell wall, surface tethering is generally performed by including spacers that allow for a certain degree of freedom to penetrate the cell wall. Jose et al. used a double aminoethoxyethoxyacetate linker combined with a 3-aminopropyltriethoxysilane modified Ti surface, which produced a vancomycin surface distance of about 4 nm [28]. However, this Ti surface coating may be prone to colonization by gram-negative bacteria such as *Escherichia coli*. Therefore, to prevent infection with various bacteria, including gram-positive and gram-negative bacteria, vancomycin may not be effective by itself. Thus, an ideal Ti implant should be fabricated to combat multiple bacterial infections.

Recently Gerits et al. [29] covalently attached a new antibacterial compound a N-alkylated 3, 6-dihalogenocarbazol 1-(sec-butylamino)-3-(3,6-dichloro-9H-carbazol-9-yl) propan-2-ol (SPI031) to the Ti surface. This showed significant antibacterial activity both in vitro and in vivo without affecting adhesion or proliferation of cells involved in osseointegration and bone repair. He et al. [30] immobilized cefotaxime sodium onto the polydopamine-coated Ti through catechol chemistry. The in vitro results demonstrated that the antibiotic-grafted Ti substrate showed good biocompatibility and well-behaved haemocompatibility. In addition, the antibiotic-grafted Ti could effectively prevent adhesion and proliferation of *Escherichia coli* (gram-negative) and *Streptococcus mutants* (gram-positive).

Antimicrobial peptides (AMP) are the host-defense peptides and they are responsible for the innate immune response found among many organisms. They present significant antibacterial, antifungal, antiparasitic and antiviral activity [31–33]. Covalent immobilization of the hLf1-11 peptide on a Ti surface reduces bacterial adhesion and biofilm formation [34,35]. KR-12 (a small peptide derived from residues 18-29 of the human cathelicidin LL protein), which has antimicrobial properties and promotes human bone marrow mesenchymal stem cell proliferation at high concentrations, was used to covalently functionalize Ti; this system significantly inhibited bacterial colonization while promoting osteogenic differentiation of human bone marrow mesenchymal stem cells [36,37].

Chitosan (CS) is also explored for immobilization onto implant surfaces to improve the biological function of osteoblasts and its antibacterial performance. Covalently immobilized chitosan onto a Ti surface can first increase the antibiotic susceptibility of bacteria, limiting the internalization of bacteria into osteoblasts and preventing implant-related infection [38]. Ti modified with chitosan-lauric acid both enhanced the biological functions of osteoblasts and reduced bacterial adhesion [39]. However, interaction with a layer of protein on the CS film can lead to the loss of the antibacterial properties of CS [40,41].

3. Use of controlled release materials around the implant

In this approach, antimicrobial-loaded materials (biodegradable or non-biodegradable) are used in the space surrounding the bone implant to enhance the local concentration of antibiotics.

There has been increasing interest in products providing local antibiotic therapy. In principle there are advantages to local antibiotic use, both for treatment and prophylaxis. Buchholz et al. first popularized the incorporation of antibiotics into polymethyl methacrylate (PMMA) bone cement for local antibiotic prophylaxis in cemented TJA [42]. Clinical studies have shown that antibiotic-loaded bone cement can decrease deep infection rates of cemented total hip arthroplasties and revision rates due to supposed "aseptic" loosening when combined with systemic antibiotic administration [43] and this solution has been found both effective and economically sound, especially in high-risk patients [44,45]. However, the pharmacokinetic profile of antibiotic released from PMMA beads is far from ideal. In vitro pharmacokinetic and in vivo animal studies demonstrated a peak local antibiotic concentration on the first day followed by a drop-off by several orders of magnitude which is known as "initial burst" release. As such, a therapeutic concentration is not maintained for the desired two to three weeks [46,47]. A second major drawback is the need for a second surgery to remove the delivery system. When left in situ for too long, the beads are actually difficult to remove. A third drawback is that the continuous low dose delivery past the first day, typically at a concentration significantly below the MIC. The extended period of slow delivery can create conditions which exacerbate bacterial resistance development potential [48,49].

Due to the problem with non-biodegradable PMMA as an antibiotic carrier, many resorbable materials have been explored for local delivery of antibiotics around the implant surface.

Collagen has been extensively explored as a carrier system for antibiotics due to its biocompatibility, low costs and availability [50,51]. Commercially available products are mainly antibiotic-loaded collagen fleeces based on collagen from bovine or equine skin or soft tendon. The collagen itself is deemed hemostyptic [52]. Most commercially available products are loaded with gentamicin and release the antibiotic relatively quickly over the first few days. In vitro studies yielded a >95% of gentamicin release from collagen fleeces within the first 1.5 hours [53].

Calcium sulfate materials have been widely used as bone void filler for long time. Different types of antibiotics, such as vancomycin, gentamicin, tobramycin and daptomycin, are incorporated within calcium sulfate to explore the application as local antibiotic delivery [54]. Calcium sulfate exhibits a very high initial burst release of approximately 45 to 80% of antibiotic content within the first 24 hours [55].

Calcium phosphate materials are widely used as osteoconductive, bone bioactive materials and have excellent biocompatibility. These materials are generally used as injectable cements or as granules. The antibiotic loading can be performed in the operating room by mixing the cement together with the antibiotic agent or by soaking the granules with a liquid antibiotic solution. An in vitro release study of commercially available bone cements showed an initial burst release of active gentamicin with a relative of gentamicin of 36 - 85% for the cements and 30 - 62% for the granules. Duration release varied from one to two weeks [56].

Local delivery of antibiotics is very attractive strategy and the local antibiotic treatment options have the potential to become major tools in the treatment of bone-associated and implant-associated infections. One promising approach can be used of antibiotic-loaded resorbable carriers along with antibiotic-eluting implant. In this regard, more studies are needed to bring a viable product in the market.

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QUESTION 2: Does the type of fixation of an arthroplasty component influence the incidence of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: There is no difference in the rates of SSIs/PJIs after total hip arthroplasty (THA) or total knee arthroplasty (TKA) based on fixation of the prosthesis.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

The type of fixation utilized for an arthroplasty gets scrutinized for its functional performance and potential to reduce the incidence of subsequent SSIs/PJIs. Below is a summary of the currently available literature on the various fixation methods for primary hip and knee arthroplasty:

Cemented, uncemented and hybrid primary THA

Several randomized control studies have compared the surgical outcomes of cemented and uncemented THA. However, most of the studies were unable to reach a conclusion on the risk of PJI based on the type of fixation due to the infrequent occurrence of SSI/PJI and low number of subjects in the cohort. Among the randomized clinical trials (RCTs) comparing cemented and uncemented THA, no difference has been observed in the rates of PJI [1-6].

Because the incidence of PJI is low, an early meta-analysis did not demonstrate a statistically significant difference in the incidence of PJI based on fixation [7]. However, a more recent meta-analysis including eight clinical studies (two RCTs and six observational studies) revealed that the incidence of PJI was 0.5% (310/67,531) in cemented group, and 0.3% (47/16,669) in uncemented group ($p = 0.008$) [8]. The use of cement in THA was associated with an increased risk of PJI (odds ratio (OR) = 1.53; 95% confidence interval (CI) 1.12 to 2.10; $p = 0.008$). The possible reasons for the higher rate of PJI in cemented THA were longer operative time and the difference in patient demographics between the two groups. However, the authors could not tell the influence of the type of cement used on the risk of PJI because five of the eight studies included did not specify whether they used antibiotic-laden bone cement or not.

The most recently published report of Phedy et al. is a meta-analysis of 27 studies attempting to show whether the infection risk is higher in cemented or uncemented prostheses. By the criteria they used, they found the current evidence is low in quality and it is hard to make a definitive conclusion based on the quality of the evidence presented [9].

Registry Data:

Evidence from large population-based studies appeared to show that the risk of revision due to PJI is roughly equal comparing uncemented with cemented fixation.

A review of this question is from the Nordic Arthroplasty Register Association for patients between 1995 and 2010 revealed no difference in infection rates for cemented vs. uncemented THA, provided antibiotic-laden cement was used (relative risk 1.5 for non-antibiotic cement) [10]. Another study using the Nordic Arthroplasty Register Association in four Nordic countries (Denmark, Finland, Norway and Sweden) observed the overall risk of revision due to infection was similar for cemented, reverse hybrid and uncemented THA [11]. Using multivariable Cox analysis, the use of cement without antibiotics and hybrid configurations were found to be risk factors for infection. Data from the Swedish Hip Arthroplasty Registry (SHAR) between 1992 and 2007 demonstrated that uncemented THA did not present a higher risk of revision due to infection compared to antibiotic-laden cemented THA [12]. Another registry study in the Finnish Arthroplasty Register observed no significant differences in the risk of early revision for infection between cemented, uncemented and hybrid THA [13]. Similar results were observed in the Danish Hip Arthroplasty Register when evaluating the rate of second revision after first-time revision of primary THA with cemented and uncemented femoral components, but did note a higher percentage of the primary THA infections were from uncemented fixation [14].

In contrast to other registry studies, the New Zealand Joint Registry on primary THA done during 1999 to 2006, found a significant increase in the risk of revision for infection in the cemented (0.36%) and hybrid group (0.32%) when compared with the uncemented group (0.22%) [15]. Importantly in New Zealand, the use of antibiotic-laden cement was uncommon during this period and 64% of the revisions for infection of cemented components were in patients who did not have antibiotic-laden cement during the primary operation. Another study of primary THA from 1987 to 2007 showed a pronounced increase in the risk of being revised due to deep infection in the subgroup of uncemented THA performed between 2003 and 2007, which had an increase of 5 times (95% CI: 2.6 – 11) compared to uncemented THA from 1987 to 1992 [16]. The authors suggested that there was a trend towards higher susceptibility to deep infection for uncemented THAs than for THAs implanted with cement-containing antibiotics.

Another study from three Norwegian health registries investigated the rate of SSI and the risk of revisions due to PJI in THA [17]. During the study period from 2005 to 2009, the rate of SSI was about 3% (167/5,540), which was not influenced by cemented or uncemented fixation. Uncemented THAs had a higher adjusted risk of revision due to PJI when compared with cemented THA (risk ratio (RR) = 1.5, 95% CI 1.0 to 2.2, $p = 0.03$). The rate of revision due to PJI for hybrid fixation was not different when compared to cemented fixation (RR = 1.1, 95% CI 1.6 to 0.7, $p = 0.7$).

A Danish Hip Arthroplasty Register found patients who had received cemented THA without antibiotics (risk ratio 1.41, 95% CI: 1.01 to 1.96) and hybrid THA (risk ratio 1.53, 95% CI: 1.19 to 1.96) had a higher risk for infection relative to uncemented implants [18]. However, the same group of researchers published contradictory results of primary THA in patients younger than 55 years of age, which found uncemented and hybrid rather than cemented implants in patients younger than 55 years had more short-term revisions associated with dislocation, periprosthetic fracture and infection [19].

The higher risk of PJI in THA using plain bone cement without antibiotics was also reported by another study from the Norwegian Arthroplasty Register Association [20]. The study directly compared

the revision rates due to infection in primary uncemented THA with those of cemented THA with antibiotic-loaded cement and to those of cemented THA without antibiotic-loaded cement. The results showed that the risk of revision due to infection was the same for uncemented and cemented arthroplasties with antibiotic-loaded cement, but higher for cemented arthroplasties without antibiotic-loaded. The authors proposed that cementation might cause bone necrosis, either by direct toxicity or by the generation of heat during the polymerization process. The necrotic bone was susceptible to the growth of bacteria, which appeared to be neutralized by adding antibiotic to the cement.

Cemented vs. Uncemented TKA

Although there are several published RCTs and systematic reviews comparing the survival of cemented versus uncemented TKA, few present PJI as the primary endpoint. A Cochrane review from 2012 comparing fixation methods in TKA was unable to report on superficial or deep infection rates due to inconsistent reporting of data in the included studies [21]. Similarly, the various retrospective studies and RCTs have not demonstrated a significant difference in the incidence of PJI between the fixation methods [22-26]. However, like the studies on THA fixation, they have low enrollments and are not appropriately powered to assess for a difference in PJI.

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QUESTION 3: Does the surface (grit-blasted, plasma-sprayed, porous metal, porous beaded and hydroxyapatite (HA) coated) of uncemented total hip arthroplasty (THA) components influence the rate of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: The surface roughness, including porosity size, geometry and symmetry determines biocompatibility. Several studies have shown that the surface material influences bacterial adherence, with an ideal pore size dependent on bacterial size. Too small a pore size does not allow bacterial lodging. In recent studies, nanotexture of material has been found to be important with some surfaces with nanotubules showing anti-infective properties.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 61%, Disagree: 20%, Abstain: 19% (Super Majority, Weak Consensus)

RATIONALE

Multiple antimicrobial coatings have been proposed in total joint arthroplasty, including silver nanoparticles, sol-gel, and hydrogel synthetics, as well as direct covalent modifications of metallic and polyethylene materials. In fact, the European Commission has recently funded a four-year initiative to establish a network of institutions involved in the development of new antimicrobial coatings to prevent healthcare-associated infections [1]. Most of those efforts so far have been limited with few implants involving antibiotic doping of hydroxyapatite (HA) layers of polyethylene with long term concerns for implant survival and antibiotic resistance development.

Nevertheless, titanium (Ti) itself comes in different forms, alloys and surfaces that may present different propensities for bacterial colonization in the face of osteointegration. Most Ti implants undergo passivation before surface modification. Passivation involves the treatment of Ti by acid, electropolishing, anodizing and oxidation. The process results in surface cleaning and removal of iron and other exogenous materials, as well as a production of a surface Ti oxide layer. The side effect of passivation is often a change in surface topography and charge. Piranha etch (H_2SO_4/H_2O_2) has been previously described for passivation but significantly changes the surface topography. Prior studies have shown that hydrothermal aging was a better way of passivating orthopaedic Ti alloys as it preserved the desired surface topography [2]. The resultant Ti oxide layer is highly biocompatible and can enhance cell adhesion and proliferation [3,4]. Increased host cell biocompatibility may result in decreased infection. Gristina et al. [5] has postulated the race for the surface describing periprosthetic infection and host cell integration/biocompatibility as competing processes and suggesting as far back as 1987 that "modifications to biomaterial surfaces at an atomic level will allow the programming of cell-to-substratum events, thereby diminishing infection."

No clear quantitative research has delineated the role of nanoscale morphology on infection [6]. Several studies have examined the interaction between the surface and various proteins. This adherent extracellular matrix directly drives and signals cell interactions at the biomaterial surface. The outer membrane of a typical cell contains many receptors that look and interact with its environment at the macro- and micromolecular levels. More than 20 members of the integrin receptor family have been identified and their interaction with motifs such as Arg-Gly-Asp (RGD) within fibronectin and vitronectin have been described [7]. These receptors interact with the surface topography including grooves and ridges [8]. Nanoscale modulation of implant surface topography can drive cell adhesion, motility, activation of tyrosine kinases and gene expression. Even though it was originally thought to be the dimensions of the topographical features that determine cell interactions, the shape and symmetry of surface features are just as crucial [4]. Zinger et al. [9] has shown an impressive variety of responses dependent on the microarchitecture of the Ti surface. Osteoblasts favored larger cavities for attachment and growth, with sub-micron-scale etching enhancing differentiation. In contrast, prostaglandin synthesis was dependent on the cavity dimensions but not the sub-micron scale. Prostaglandins are important in cellular response to infection, and thus surface topography may modulate periprosthetic infection.

Interestingly, bacteria have also been shown to interact with the surface, frequently exhibiting similar propensities for biomaterials as osteoblasts. Truong et al. [10] have shown that *S. aureus* had a preference for granular Ti surfaces while *Pseudomonas* preferred polished surfaces. Singh et al. [6] show that the increase in surface pore aspect ratio and volume, related to the increase of surface roughness, improves protein adsorption, which in turn downplays bacterial adhesion and biofilm formation. As roughness increases up to about 20 nm, bacterial adhesion and biofilm formation are enhanced; further increase of roughness causes a significant decrease of bacterial adhesion and inhibits biofilm formation. Lorenzetti et al. [11] suggest that the pore size correlates to the size of the bacteria, where in, too small a size does not allow bacterial lodging into the space while too large a size does not allow the bacteria to hide from the surrounding environment and the host. Studies have shown that over 90% of *S. aureus* express either fibronectin binding proteins, fibrinogen binding proteins or collagen binding proteins, with almost 60% of bacteria expressing all of these proteins [12]. More worrisome, these genes were significantly more common in methicillin-resistant *S. aureus* (MRSA) than in susceptible strains. These cell surface receptors give bacteria an advantage for surface and extracellular matrix interactions that ultimately may allow them to outcompete osteoblasts for surface propagation.

The differential response of osteoblasts and bacteria to titanium topography raises the question regarding the specific interactions on commercially available titanium surfaces. Modern implants have gone through several iterations of surface topography changes, most recently with three-dimensional printing. Surface roughening of titanium produces topography that is biocompatible and improves osteoblast adhesion, proliferation and differentiation [13]. Much less is known about the bacterial response to these surfaces.

Grit blasting involves pressurized particle projection using ceramic or silica materials onto the implant surface. The process always involves a subsequent acid etching to remove any contaminants that could have been deposited on the surface. Al-Radha et al. [14] have examined the effect of zirconia, Ti blasted with zirconia, Ti blasted with zirconia followed by acid-etching, as well as polished Ti surfaces on bacterial colonization. The Ti blasted with zirconia reportedly showed lower bacterial adhesion, but that was in the presence of saliva. The base surfaces showed no difference in terms of bacterial colonization, even between polished and blasted surfaces. The average surface roughness in this study was about 0.16 um for the zirconia blasted surfaces.

Plasma spray coating involves thick layer deposition of materials such as Ti or HA, usually by spraying the melted material onto the substrate. Plasma spray is theoretically better controlled than grit blasting and exhibits the highest surface roughness compared to acid etching or grit blasting. Knabe et al. [15] report an average roughness of 3.43 um for plasma sprayed Ti and 2.07 for HA coated Ti. Interestingly, they also show that HA sprayed surfaces had significantly less bone contact.

HA coating is used for total hip coatings due to its presence in normal bone and the potential biocompatibility and osteoconductivity. Synthetic calcium phosphate ceramics have similar chemical and crystalline properties to biological apatite crystals. HA is the most similar to biological crystals while being the least soluble of all calcium phosphate ceramics [16]. Interestingly, in an analysis of 116,069 THAs using the Nordic Arthroplasty Register Association database, Hailer et al, [17] found no difference in revision rate between HA coated and uncemented porous or rough sand-blasted stems. Despite extensive mentioning of anti-infective properties of HA coating in the literature, the potential benefit would only be secondary to possible earlier osteoblast deposition on the surface, with no clear antibacterial effects studied or reported.

Ultimately, most studies of surface topography, surface roughening and implant surface design focus primarily on osteocompatibility. Even though surface roughness influences bacterial adhesion and survival, we were not able to identify any well controlled studies on bacterial growth on different orthopaedic implant topographies. Large registry studies show largely no difference of survival between various implants. Perhaps the material itself, such as tantalum [18], may provide an advantage in the face of periprosthetic infection. Nevertheless, roughened Ti surfaces definitely provide an osteoconductive advantage. Considering the "race for the surface" theory, such materials should then provide a certain competitive advantage against infection, even though we have a hard time recommending a specific surface topography at this time. Further research, new techniques in surface preparation, and the advantage of designer surfaces will likely allow for further delineation of this question in the near future.

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QUESTION 4: Does the type of bearing surface influence the incidence of surgical site infections/periprosthetic joint infections (SSIs/PJIs) after total hip arthroplasty (THA)?

RECOMMENDATION: There is a higher incidence of PJIs with metal-on-metal (MoM) THA; however, there is no difference in risk of PJIs among other bearing surfaces.

LEVEL OF EVIDENCE: Strong

DELEGATE VOTE: Agree: 84%, Disagree: 10%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

THA bearing surfaces have been developed primarily to optimize wear properties. However, there has been recent interest in differing propensities for infections among bearing types. It has been hypothesized that some bearing couples may have a disproportionately negative influence on local tissue immunocompetence, resulting in development of clinically manifested PJI that would otherwise remain silent [1].

In a study of 276,878 patients from the Australian Orthopaedic Association National Joint Replacement Registry, a higher rate of revision for PJI was observed with large-head MoM THA as compared to other bearing surfaces [2]. In a smaller retrospective case series of 124 patients, MoM THA had a 4-fold higher infection rate than historical cohorts of other bearing surfaces from the same institution [3]. Furthermore, Lee et al. performed a meta-analysis comparing MoM to ceramic-on-ceramic bearings, finding MoM bearings were associated with a higher risk of revision for PJI (odds ratio (OR) = 6.21, p = 0.015) [4].

Multiple prospective randomized trials, as well as a systematic review/meta-analysis, have demonstrated no difference in infection rate between metal-on-polyethylene, ceramic-on-ceramic, and ceramic-on-polyethylene bearings [5–8]. Hu et al. performed a meta-analysis of five randomized controlled trials comparing ceramic-on-ceramic and metal-on-polyethylene bearings and found no difference in deep infection rate [9]. A registry study by Pitto et al. found ceramic-on-ceramic bearings to have a lower risk of revision for PJI compared to other bearings [10]. However, this work did not incorporate Body Mass Index or medical comorbidities into its multivariate analysis, which are known to have a significant effect on PJI risk [11].

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QUESTION 5: Does the use of a modular femoral neck implants during primary total hip arthroplasty (THA) affect the risks of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: Modular femoral neck implants are associated with increased revision rates due to hardware failure, metal corrosion and adverse local tissue reaction (ALTR). In patients with failed THA as a result of use of a modular femoral neck, a higher incidence of subsequent SSIs/PJIs is expected.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 72%, Disagree: 21%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

Modular femoral neck systems were introduced as an alternative to fixed neck systems to allow surgeons better ability to restore the biomechanics of the hip including neck angle, offset, anteversion and leg length [1,2]. However, modular femoral neck THA implants are associated with high early revision rates and poor long-term survivorships [3–8]. Reported modes of failure include hardware fracture [9–12], aseptic loosening [13] and metal corrosion resulting in ALTR [14–21]. In fact, some designs have been recalled because of high revision rates as a result of metal debris from the modular junction [3,6,22]. The additional metal junction is vulnerable to mechanical failure, component disassociation, mechanically assisted crevice corrosion (MACC) as well as metal ion release [4,5,14,17,19,20]. All modular junctions have the potential to release metal ions as a result of corrosion, wear and micromovement [2,15,18,21,23,24].

Previous literature has suggested that metal-on-metal (MoM) bearing surfaces in THA predisposed patients to higher infection rates when compared with other bearing surfaces [25–31]. It has been posited that MoM wear and corrosion particles could change the periprosthetic environment and increase the risk of infection [29]. Potential reasons for this increased risk include changes in the immune system by wear particles such as reduced cell proliferation [29,30,32]. Since modular femoral neck systems release metal wear particles and produce ALTR similar to MoM implants, are they also at risk of increased rate of PJI?

A comprehensive analysis of the incidence of SSI or PJI after the use of modular femoral necks in primary THA has not been published. Thus, the available evidence on this topic is low-level.

Duwelius et al. compared 284 patients with non-modular stems to 594 patients with modular neck stems performed by one surgeon and with similar demographics [1]. There were no statistically significant differences in either deep or superficial infection at a mean follow-up of 2.4 years (0.7% PJI in modular group vs. 1.4% in non-modular group). Furthermore, in a review of the Australian Orthopaedic Association National Joint Replacement Registry data, there was no difference in the rate of revision for infection for modular neck prostheses (0.7% of 9,289 modular neck primary THAs) compared with non-modular prostheses (0.6% of 253,165 non modular primary THAs) [8].

With the limited literature available, the presence of a modular femoral neck does not appear to increase the risk of SSI/PJI in primary THA. However, it is important to note that the clinical presentation of ALTR caused by a modular neck prostheses, head-neck junction, or MoM articulation, may mimic that of infection, and is in fact associated with a higher incidence of PJI [27,33,34] and can cause a false positive alpha-defensin test [35,36]. For this reason, gross purulence was removed from the PJI diagnostic criteria given its low specificity for PJI [37]. Thus, the reason for revision may have been misdiagnosed in some cases. In addition, many of the articles reporting higher incidence of PJI in the MoM population were before the wide acceptance of the MusculoSkeletal Infection Society/International Consensus Meeting (MSIS/ICM) definition of PJI or are Medicare database studies. PJI must be included in the differential diagnosis of all symptomatic modular femoral neck THA using recently established criteria [38].

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QUESTION 6: Can implant factors (i.e., type of bearing) influence the thresholds for serum and synovial markers in acute and chronic periprosthetic joint infections (PJIs)?

RECOMMENDATION: Yes. Different bearing surfaces such as metal-on-metal (MoM), metal-on-polyethylene and dual taper modular stems in the setting of taper corrosion can influence the serum and synovial markers. Metal debris may interfere with automated cell counts. Manual cell counts are preferred when evaluating patients for PJIs who have elevated synovial fluid metal levels. Optimal thresholds for serum and synovial markers for diagnosing PJIs in these settings still need to be established.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Implant factors such as bearing surfaces can influence serum and synovial markers when evaluating for PJIs. This has been mostly studied in MoM bearings and dual taper modular stems [1–3]. It can be difficult to discern adverse local tissue reactions (ALTRs) with associated metal ion release from inflammatory response to infection [4,5]. However, it is important to determine the presence of infection as it will alter treatment [6,7]. Serum erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and white blood cell (WBC) count with differential are important tests in helping determine presence of PJI [8].

There have been various recommendations regarding the parameters for serum and synovial markers for diagnosing PJI in the presence of MoM corrosion, but most studies have demonstrated that the type of bearing surface and other implant factors can affect the thresholds for serum and synovial markers in PJI. Still, no literature has clearly delineated the specific parameters that should be utilized for differing bearing surfaces to diagnose PJI [9,10].

Automated synovial cell counts and differentials in the setting of a failed MoM THA have been reported to be inaccurate [2,3,11]. It has been theorized that the automated cell counting machine may be incorrectly identifying particulate debris and counting it as cellular [2]. As such, many surgeons propose utilizing a manual cell count and differential when analyzing the synovial WBC and differential [1].

Wyles et al. [2] found that the sensitivity of the synovial WBC count could be maintained at 100% while improving specificity to 71% if the cutoff to diagnose infection was moved from >3,000 to >15,000 cells/microliter. Additionally, the authors found the sensitivity of neutrophil percentage could be maintained at 100% and improved specificity to 100% by elevating the cutoff percentage from 82 to 92% neutrophils. Regarding CRP, the authors found that the sensitivity of CRP could be maintained at 75% while improving the specificity of CRP to 97% if the cutoff value of CRP was raised from >8 to >54 mg/L. The authors demonstrated that changing the cutoff value for the ESR did not change specificity as significantly.

In contrast, Yi et al. [3] studied PJI in patients with failed MoM bearing surfaces and after excluding what they deemed to be inaccuracies, recommended a synovial WBC cutoff of 4,350 WBC/microliter with 100% sensitivity and 95% specificity. The authors, however, reported low positive predictive values of 43% and 39% for ESR and CRP, respectively, in the setting of MoM bearings.

Kwon et al. reported that ESR and CRP have a limited value in the diagnosis of PJI in dual taper modular implants with evidence of corrosion, but acknowledged the utility of ESR and CRP in excluding PJI [1]. The authors demonstrated, however, that synovial WBC and differential were useful markers for diagnosing infection. Specifically, the authors demonstrated a sensitivity and specificity of 86% and 80%, respectively, when utilizing a synovial WBC cutoff of 730 cells/microliter. A synovial polymorphonuclear (PMN) % cutoff of 65% yielded a 100% sensitivity and a 70% sensitivity.

Okroj et al. in a multicenter study evaluated the alpha-defensin test to diagnose PJI in the setting of ALTRs. Twenty-six patients were reviewed with one of 26 (3.8%) meeting the MusculoSkeletal Infection Society (MSIS) criteria for PJI. The one patient with PJI had a metal-on-polyethylene bearing surface with head-neck taper corrosion. Of note, there were 8 falsely positive alpha-defensin tests. The authors concluded that in the setting on ALTRs, alpha-defensin testing can lead to a high rate of false positives [12].

Though the exact parameters to diagnose PJI in the setting of different implant factors need further elucidation, given the existing literature, we conclude that various implant factors can influence both synovial and serum markers in the setting of PJI. We strongly urge the orthopaedic community to be cognizant of the influence of bearing surfaces, especially in the setting of MoM implants or potential metal corrosion, and to consider using a combination of diagnostic tests along with manual cell counts as part of their PJI diagnostic workup.

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QUESTION 7: What can be done with a prosthesis that has been dropped on the floor or allowed to come into contact with a non-sterile portion of the operating room?

RECOMMENDATION: Cleaning, re-sterilization and reuse of dropped prostheses or implants is not permitted in most hospitals and should not be performed. Only in extremely rare circumstances, such as the use of a custom implant, a dropped prosthesis may be decontaminated and sterilized.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

The creation and maintenance of an aseptic environment has a direct influence on patient outcomes in general and the incidence of subsequent surgical site infections/periprosthetic joint infections (SSIs/PJIs) in particular. One of the measures for preventing SSIs is to provide surgical instruments and implants that are free of contamination at the time of use [1]. This is particularly important when an implant such as a joint prosthesis is being left behind in the body. Prior studies have shown that as little as 100 bacteria gaining access to a surgical field that involves the use of an implant is sufficient to lead to infection [2,3]. The number of bacteria needed to result in infection in the absence of an implant was much higher [4,5]. Thus, the presence of a foreign material, such as an implant, is a strong risk factor for subsequent SSIs/PJIs [4,5]. Due to this, extreme care should be exercised in ensuring that the prosthesis being implanted in joints are completely sterile and devoid of any bacteria [6].

There are strict regulatory requirements for implant sterilization, which is usually the last step in manufacturing of these prostheses [7]. Most manufacturers use high dose gamma irradiation to achieve the required sterility of implants manufactured for use in humans [6]. Implants being opened from their package are thus believed to be absolutely sterile. Dropping an implant on the floor results in contamination of the implant by microorganisms that can potentially lead to a subsequent infection. Sterilization of the dropped implants in the hospital using autoclave does not meet the regulatory requirements and very likely leads to presence of residual bacteria or their cell walls "exotoxins" [8]. Thus, this practice is not considered to be acceptable by hospitals and local health authorities.

Different sterilization methods, such as steam, dry-heat, ethylene oxide, formaldehyde or ionizing radiations result in a different effect on the biomaterial surface and their subsequent behavior in vivo [9]. Titanium (Ti) has been widely used as an implant material due to its biocompatibility and excellent corrosion resistance. In order to enhance osseointegration of dental and orthopaedic implants made of Ti, many surface modification strategies have been pursued, focusing on the important role of the biomaterial surface properties [6].

Annunziata et al. evaluated the effects of the argon plasma treatment on different Ti implant surfaces previously exposed in vitro to bacterial contamination. They found that the argon plasma technology could be efficiently used to decontaminate/sterilize previously contaminated Ti implant surfaces [7], however, they did not evaluate any possible adverse effect of sterilizing method on implant characteristics. Park et al. evaluated the effect of cleaning and sterilization on Ti implant surface properties and cellular response. In their study, different methods for Ti sterilization that included autoclaving, gamma irradiation, oxygen plasma, and ultraviolet were used [6]. The study indicated that recleaning and resterilized Ti implant resulted in surface alterations that could potentially affect the osseointegration of the surface and other biological behavior of the biomaterial in vivo.

Based on the latter study, we conclude that resterilization of dropped components in a hospital setting could lead to detrimental alteration of the biomaterial surface of the implant being used and adversely affect the in vivo behavior of the implant. Thus, and whenever possible, a new implant should be used to replace the dropped implant. If this is not possible, the dropped implant needs to be processed very carefully to remove all potential microorganisms on the surface [10]. This may include chemical cleansing of the implant with bactericidal agents such as chlorhexidine or povidone iodine. The purpose of cleaning is to remove or reduce visible soils, blood, proteins and debris [11]. To resterilize the implant, it should be subjected to steam-heat, as irradiation method for sterilization is not available in hospitals. Flash sterilization is not recommended [1]. The wound should also be copiously irrigated with antiseptic solution, such as aqueous povidone iodine, prior to the use of the dropped implant.

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1.8. PREVENTION: POSTOPERATIVE ISSUES

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QUESTION 1: Should patients with cellulitis following total joint arthroplasty be treated with antibiotic therapy?

RECOMMENDATION: Yes. When periprosthetic joint infection (PJI) has been ruled out, it is reasonable to treat patients presenting with cellulitis with empiric antibiotics.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Much of the literature relating to infectious postoperative complications relates to deep PJIs. Postoperative cellulitis is a rare, yet realistic complication that may occur following arthroplasty. The concern for cellulitis is that the superficial infection may spread to the deeper tissues including the prosthetic joint. Thus, the presence of cellulitis in patients with a prosthetic joint is considered to be a serious issue.

All the literature relating to the treatment of superficial infections relates to hip and knee arthroplasty. Many of the studies in this area are of non-randomized, retrospective designs. Much of the literature related to surgical site infections (SSIs) in total joint arthroplasty is epidemiological in nature, focusing on incidence and risk factors, rather than treatment and outcomes. Perhaps reflecting the diagnostic dilemma facing physicians, there appears to be much heterogeneity in the literature in defining the diagnosis of cellulitis versus inflammation versus superficial SSIs.

The largest prospectively gathered dataset regarding superficial wound infections has been described by Guirro et al. in a Spanish cohort following total knee arthroplasty (TKA) [1,2]. They highlight 45 cases of superficial wound infections in a larger series of 3,000 joints with six years follow-up, without any evidence of recurrence of infection or progression to deeper periprosthetic infections. Of note, is that six (13.3%) of these patients also required surgical treatment in the form of wound irrigation and debridement in addition to antibiotic therapy. Interestingly, three of these patients required later revision arthroplasty for non-infectious causes.

The occurrence of an erythematous, erysipelas-like manifestation after total hip arthroplasty (THA) has been described in two publications [3,4]. A total of 17 patients across both publications were described as successfully treated with antibiotics following an erythematous eruption around the incision and the gluteal area. There was no evidence of a deep infection at last follow-up.

Walls et al. described a case series of methicillin-resistant *Staphylococcus aureus* (MRSA) SSIs following primary hip arthroplasty [5]. Out of 1,790 hips performed over a five-year period, 18 (1%) were described as having MRSA SSIs. Six of these 18 were defined as superficial infections. Five were treated successfully with antibiotics, while one patient returned after seven months with a deep infection.

The other series described in relation to TKA has been published by Manian et al. [6]. Of note, this was a retrospective case series evaluating post-arthroplasty patients presenting with any form of soft tissue or skin bacterial infection in the lower limb. Interestingly, at a mean of 65 months postoperatively, patients were statistically more likely to present with cellulitis in the operated limb than their contralateral leg. They did not define their treatment outcomes.

It is clear from this discussion that there is a marked heterogeneity in the literature regarding the use of antibiotics in patients with cellulitis post-arthroplasty. Without clear consensus on defining the diagnosis, in addition to the myriad of study methodologies, the data is not amenable to meta-analysis. To determine a more robust consensus on this question, further prospective randomized trials are recommended.

In the absence of such studies and evidence, we feel that cellulitis is a serious event in patients with a prosthetic joint in place and requires treatment. However, to distinguish cellulitis or superficial infection from PJI is a difficult task in a majority of patients. As missing the diagnosis of PJI may result in suboptimal outcomes for patients because they are not usually amenable to treatment with antibiotics alone, we recommend that any patient presenting with cellulitis or presumed superficial infection undergo an evaluation for a PJI, which may include aspiration of the joint in order to rule out a PJI prior to empiric antibiotic treatment.

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QUESTION 2: Is undergoing a colonoscopy or upper gastrointestinal (GI) endoscopy after total joint arthroplasty (TJA) associated with an increased risk of surgical site infection/periprosthetic joint infection (SSI/PJI)? If yes, does antibiotic prophylaxis prior to a colonoscopy or upper GI endoscopy after TJA reduce the risk?

RECOMMENDATION: Colonoscopy and upper GI endoscopy have the potential to cause transient bacteremia, though the evidence is limited to support an associated risk of SSI/PJI. There is no evidence that administration of antibiotics prior to GI procedures decreases the risk of SSI/PJI and this practice should be avoided. Further research is needed to see if this practice may be beneficial in selected or high-risk patients.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Transient bacteremia can occur with many procedures, including periodontal manipulation, barium enema and GI and genitourinary (GU) procedures. Endoscopic procedures, including colonoscopy and esophago-gastro-duodenoscopy (EGD), are frequently associated with transient bacteremia [1–5]. The incidence of bacteremia after standard colonoscopy has been estimated to be between 0 and 5% [6]. Rates of bacteremia increase when endoscopy is accompanied by instrumentation and tissue manipulation, such as biopsy or polypectomy and the incidence of bacteremia differs by procedure: flexible sigmoidoscopy 0.5%, colonoscopy 2.2%, EGD 4.2%, variceal ligation 8.9%, endoscopic retrograde cholangiopancreatography (ERCP) 11%, variceal sclerotherapy 15.4% and esophageal dilation 22.8% [7]. Another study showed similar results with the highest rates of bacteremia occurring with dilation of esophageal strictures and sclerotherapy of esophageal varices (approaching 45%) [2].

Although it is recognized that transient bacteremia does occur after GI endoscopic procedures, the same phenomenon occurs frequently during routine daily activity, often at rates exceeding those associated with endoscopy. EGD with dilation has been associated with transient bacteremia rates of 12 to 22% [7,8], whereas, brushing and flossing teeth has been associated with bacteremia rates between 20 to 68%. Even routine activities such as mastication have been associated with bacteremia rates of 7 to 51% [9]. These high rates compared to the relatively low frequency of bacteremia in patients undergoing GI procedures has been the rationale for the American Society for Gastrointestinal Endoscopy (ASGE) advocating that routine prophylactic antibiotics prior to endoscopic procedures in patients with orthopaedic implants is not required [10].

Evidence is lacking to support an increased risk of SSI/PJI from colonoscopy or upper GI endoscopy. There is one prospective single-center, case-control study conducted by Coelho-Prabhu et al. that found a possible increased risk of PJIs among patients undergoing EGD with biopsy (odds ratio (OR) =3, 95% confidence interval (CI): 1.1-7) [4]. Cases were defined as adult patients hospitalized for PJI of the hip or knee between 2001 and 2006. Controls were adults with hip or knee arthroplasty without a diagnosis of joint infection who were admitted during the same interval. There were 339 identified cases and 339 controls. The primary outcome measure was the odds ratio of PJI after a GI endoscopic procedure performed within the last 2 years. Procedures included flexible sigmoidoscopy, esophageal dilatation and EGD and colonoscopy both with and without biopsy. Overall, there were 21% of case patients who underwent a procedure vs. 24% among the controls. Among the procedures, only EGD with biopsy was found to have a significant association with PJI. EGD with biopsy had occurred in 19 (6%) of cases and 8 (2%) of controls (OR 2.8). After adjusting for various risk factors, the OR for PJI after EGD with biopsy was 3.8 (95% CI: 1.5-9.7). Among the PJI cases, there was no significant difference in the microbiology of PJI between the group who had undergone endoscopy and the group that did not. Both groups had coagulase-negative *Staphylococcus* species and *Staphylococcus aureus (S. aureus)* as the most common organisms, whereas, bacteria colonizing the GI tract comprised only 17% of PJIs in both.

Another study by Ainscow et al. prospectively studied 1,000 patients who underwent 1,112 hip and knee arthroplasties over six years [11]. These patients were not advised to take antibiotic prophylaxis for subsequent dental or surgical procedures. A total of 224 had undergone dental or surgical procedures. Only three cases of hematogenous infection had developed during the study period, all from a skin or soft tissue infection source [11].

In addition to the above, there have been only four case reports in the literature describing a PJI that occurred within 12 hours to 2 weeks of an endoscopic procedure [12–15]. The bacterial pathogens that were believed to have hematogenously spread to the prosthetic joint in these cases included *Streptococcus milleri*, *Group B streptococcus, Listeria monocytogenes,* and *Serratia marcescens*. Notably, these case reports were published from 1990 to 2003, when orthopaedic and gastroenterological practices differed from the current practices in 2018.

In summary, there is no clinical evidence that giving prophylactic antibiotics decreases the risk of SSI/PJI after colonoscopy or upper GI endoscopy procedures. Before deciding to give antibiotic prophylaxis, clinicians must evaluate each patient individually based on the risk factors and type of procedure and balance the benefits of antibiotic prophylaxis with the risks of increasing bacterial resistance, adverse side-effects and drug interactions.

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Diagnosis

2.1. DIAGNOSIS: DEFINITIONS

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QUESTION 1: What is the definition of a periprosthetic joint infection (PJI) of the knee and the hip? Can the same criteria be used for both joints?

RECOMMENDATION: See Figure 1, Proposed 2018 International Consensus Meeting (ICM) criteria for PJI.

Major Criteria (at least one of the following)	Decision
Two positive growths of the same organism using standard culture methods	Infected
Sinus tract with evidence of communication to the joint or visualization of the prosthesis	

Minor Criteria	Threshold		Score	Decision
	Acute€	Chronic		
Serum CRP (mg/L) *or* D-Dimer (ug/L)	100 Unknown	10 860	2	Combined preoperative and postoperative score: ≥6 Infected 3 to 5 Inconclusive* <3 Not Infected
Elevated Serum ESR (mm/hr)	No role	30	1	
Elevated Synovial WBC (cells/µL) *or* Leukocyte Esterase *or* Positive Alpha-defensin (signal/cutoff)	10,000 ++ 1.0	3,000 ++ 1.0	3	
Elevated Synovial PMN (%)	90	70	2	
Single Positive Culture			2	
Positive Histology			3	
Positive Intraoperative Purulence¥			3	

€This criteria were never validated on acute infections. ¥ No role in suspected adverse local tissue reaction.
*Consider further molecular diagnostics such as next-generation sequencing

FIGURE 1. Proposed 2018 ICM Criteria for PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 68%, Disagree: 28%, Abstain: 4% (Super Majority, Weak Consensus)

RATIONALE

The introduction of the MusculoSkeletal Infection Society (MSIS) criteria for PJIs in 2011, which was later altered by the 2013 ICM, resulted in immense improvements in diagnostic confidence and research collaboration [1]. In recent years, numerous serum and synovial markers have been evaluated and have become widely available [2–14]. Moreover, publications in recent years show different sensitivities and specificities for the various tests used [4,14] and highlight the value of a high pretest probability in the overall diagnosis [9,15,16]. These advancements in the field call for the modification of current diagnostic criteria to an evidence-based one.

In a recent multi-institutional study [17], we proposed a new definition considering the relative and quantitative weight of established, as well as newer, markers [7,9,11]. The new diagnostic criteria also consider chronicity and invasiveness of the diagnostic tests, making the preoperative diagnosis of infection easier compared to previous definitions. By using a stepwise approach in developing the current criteria which was based on the current American Academy of Orthopaedic Surgeons (AAOS) guidelines [18], we were able to provide relative weights for each diagnostic marker/finding. The threshold for infection of the combined score was determined in a way that would keep false positives to a minimum (threshold for infection), but also reduce false negatives (threshold for not infected). By performing this in a stepwise manner, we were able to maximize sensitivity in early stages of the workup (to avoid under-diagnoses), as well as to maximize specificity in later stages (to avoid over-diagnoses).

This proposed definition showed a high level of performance using an independent multi-institutional cohort for validation and a better performance compared to previous MSIS and ICM definitions. The new criteria demonstrated a sensitivity of 97.7% compared to the MSIS (79.3%) and ICM definition (86.9%), with a similar specificity of 99.5%. It also enabled one to reach an earlier diagnosis compared to previous criteria, as more than 80% of the PJI cases using the new definition were diagnosed prior to surgery. This enhanced the importance of a joint aspiration prior to surgery and supported it in becoming the cornerstone of diagnosing PJIs. Another novel finding of the present definition is the introduction of patients in which a diagnosis is inconclusive. These patients are often encountered in clinical practice and represent a real diagnostic challenge. Pointing out this unique group or "gray area" of patients promotes awareness in both clinical practice and the need for further research focused on this cohort.

ICM Discussion and Controversies

The criteria have been reviewed and altered by a group of recognized international experts who were also delegates of the ICM. This question and the proposed criteria have been discussed and debated extensively during the ICM and reached only a weak consensus, with 28% disagreeing with it. Our group wishes to point out some important clarifications and controversies that were raised during the meeting:

1. The proposed definition was developed and validated on a cohort with chronic PJIs. Patients with acute PJIs and acute hematogenous PJIs (with < 6 weeks of symptoms) were excluded from this study since we were not able to define a proper control group for them. A control group for acute infections would be patients following joint arthroplasty undergoing a serum and synovial fluid investigation, but proven to not be infected—isolating and defining the control cohort is challenging and rare. Different thresholds for acute infections have been suggested in the literature and we used the previous ICM thresholds for the parameters used. While we believe these new criteria should apply also for acute and acute hematogenous infections, both the scoring system and the proposed thresholds require further validation on this specific population.
2. The proposed criteria may under-diagnose less overt infections. Defining PJIs based on major criteria for developing the scoring system may have affected the thresholds of different markers and has the potential to under-diagnose more overt infections. That being said, 30% of the cohort used for developing the scoring system had Coagulase-negative Staphylococcus (CoNS), which is not considered to cause a major immune response. Moreover, we validated the scoring system on an external cohort of infected and non-infected patients, independent from any previous criteria. In this group of patients, there were many culture negatives as well as so called "low grade infections," and the new criteria demonstrated a high sensitivity of 97.7%. Future research should be aimed on validating the utility of the new definition in more overt infections.
3. For the current definition, a decision tree index (Gini) was used to point out the thresholds for the various markers evaluated that would provide maximal sensitivity and specificity for each marker based on chronicity and the pretest probability. When these thresholds were similar to the previous ICM definition, we used the earlier one to ease its implementation. It should be pointed out that a variety of thresholds have been proposed in the literature and may be different from the ones proposed here. These differences may be attributed to the fact that we wanted to maximize sensitivity in early stages of the workup and to maximize specificity in more advanced stages.
4. The new diagnostic criteria were originally validated on patients from three major orthopaedic institutes in the United States. Additionally, since its introduction earlier this year, the criteria have been validated in patients treated in Japan and Brazil, as well as 84 patients from around the globe using a designated chatbot. They need to be further tested and validated in large volume centers outside the USA to assess whether the preliminary findings presented above are indeed accurate.
5. Several delegates have raised the issue that alpha-defensin is an expensive test that should not be performed routinely. We would like to emphasize that the present scoring system is not designed or intended to be used as a guide for which tests should be ordered; rather, it should be used as a tool to diagnose patients when a panel of tests are already available. Not all tests are needed to use this proposed definition and a preoperative diagnosis can be made without the need for intraoperative findings. To further clarify this issue, we have combined the two tables from the original criteria (separating preoperative and intraoperative findings) into one table.
6. In the present study, we used conventional cultures to diagnose and to define positive growth. We did not use sonication or novel techniques such as Next Generation Sequencing. More sensitive microbiological investigation methods are likely to reveal a potential infection in the absence of elevated serum and/or synovial markers. As these novel methods for isolation of organisms become more widespread, the newly proposed criteria should be validated once again.

7. The proposed definition was developed and validated on both PJI cases of the knee and the hip. While several publications have noted differences in the thresholds for synovial markers in PJI cases of the hip and the knee, we believe the differences are minor. Thus, the new definition has not made a distinction between hip and knee PJI. Nevertheless, future studies should explore such potential difference between these two joints.
8. Newer markers, such as the serum D-dimer, have not been sufficiently studied and while we had sufficient data to analyze the new markers and include them in the definition – more work is needed to further validate their role in the diagnosis of PJIs. Moreover, their role and thresholds in diagnosing acute PJIs still remains unknown.
9. In patients with adverse local tissue reactions (ALTRs), crystalline deposition arthropathy, inflammatory arthropathy flares, infections with slow-growing organisms and patients under antibiotic treatment, the proposed criteria may be inaccurate.
10. There may be other situations when a patient is infected and does not meet the diagnostic criteria and vice versa. Clinical judgment should still prevail and guide physicians in the management of patients.

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QUESTION 2: What is the definition of septic arthritis in a native knee?

RECOMMENDATION: Native septic arthritis of the knee is a clinical diagnosis supplemented by relevant laboratory data. Signs of septic arthritis include painful effusion, limited range of motion and warmth. Elevated serum inflammatory markers, particularly C-reactive protein (CRP), synovial white blood cell (WBC) counts (50,000 cells/mm^3), polymorphonuclear (PMN) cell count percentages (> 90%) and purulent appearance of the synovial fluid indicate a high likelihood of septic arthritis.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 7%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Native septic arthritis of the knee classically presents with a painful effusion and limited range of motion. Diagnosis of this clinical entity cannot be made on the basis of laboratory data alone, with infections occurring in the presence of negative cultures and absent in the presence of markedly elevated intra-articular cell counts [1]. The frequency of native knee septic arthritis appears to be increasing and major concerns for serious medical complications and mortality persist [2]. The most robust information on laboratory data diagnostic for septic arthritis is available for the pediatric hip joint [3,4]. However, such high-quality, algorithmically predictive data is lacking for the adult native knee joint.

Septic arthritis in the knee remains a challenging diagnosis to make due to similarities to other entities in clinical presentation and equivocal laboratory results. Clinical impression remains the mainstay of diagnosis, but should be supplemented by relevant laboratory data. Screening inflammatory markers, particularly a

CRP, should be obtained and suspicion for infection should always be kept to avoid missing a diagnosis. Aspiration of the knee should be completed prior to administration of antibiotics when clinically feasible to increase diagnostic accuracy. Synovial cell counts greater than 50,000 cells/mm^3 and/or PMN cell count percentages greater than 90% indicate a high likelihood of septic arthritis [5].

Laboratory data obtained where clinical suspicion for septic arthritis exist includes serum erythrocyte sedimentation rate (ESR) and CRP. While lacking specificity, a CRP elevated above 10.5mg/dL has been demonstrated to show a high correlation with septic arthritis in native joints in the appropriate clinical scenario [6]. A study by Hügle et al. also indicates that procalcitonin (PCT) is useful for establishing the presence of infection and may have superior sensitivity and specificity than CRP in detecting septic arthritis [7].

Aspiration is a critical portion in evaluating the possibility of native knee septic arthritis. Numerous studies and a meta-analyses have shown higher synovial WBC counts more likely to represent infection [8] and greater percentage of PMN cells (> 90%) highly predictive of septic arthritis [5]. Traditional teaching held that cell counts could be divided into non-inflammatory, inflammatory and infectious, corresponding to 0 to 2,000 cells/mm^3, 2000 to 50,000, and >50,000, respectively. However, one investigation showed only 64% sensitivity of using this infectious cell count cutoff, with approximately one-third of patients with septic arthritis having a cell count lower than 50,000 [9]. Therefore, infection can also be present with lower cell counts and gross inspection of the fluid can be as valuable as the cell count in determining infectious pathology of an effusion [10,11]. In particular, synovial WBC count more than 50,000 and percentage of PMN more than 90% provide adequate concern to identify septic arthritis while waiting for culture test results [5].

A native knee aspiration resulting in a false positive culture is rare if done under proper technique. Jennings et al. demonstrated a false positive rate of 0% of 166 knees in their series using appropriate sterile technique [12]. Therefore, positive cultures obtained using such technique should raise the alarm for the high likelihood of a real infection. Administration of antibiotics prior to obtaining an aspiration has been shown by Hindle et al. to decrease the yield for culture and to reduce its accuracy from 79 to 28%, and should be avoided when feasible [13]. The available literature suggests that Staphylococcal species are the most common causative organisms for septic arthritis of the knee in an adult, followed by other gram-positive cocci and gram-negative bacilli [2,14]. However, septic arthritis by other atypical organisms can occur and this needs to be kept in mind when investigating patients with suspected septic arthritis.

The leukocyte esterase (LE) test is used commonly for diagnosis of infections in different organs [15]. In a recent prospective study of 27 cases of acute monoarticular arthritis in major joints, Gautam et al. reported a 100% sensitivity of the LE test in the diagnosis of septic arthritis when +2 was considered indicative of a positive result. The positive predictive value in their series was 94% and only one synovial sample was LE positive despite negative culture results. They concluded that this test could efficiently differentiate other etiologies of inflammatory acute arthritis from septic arthritis [6]. Another study by Ceja-Picazo et al. had almost identical findings and supported the use of LE dip stick in investigation of patients with painful knee and suspected of septic arthritis, as it was able to differentiate osteoarthritic from infected knees [16].

The role of molecular techniques such as polymerase chain reaction (PCR) has been previously investigated in the diagnosis of septic arthritis. The studies have found that PCR may not provide additional data to culture in investigation of these patients [17]. However, as time has progressed and technology has improved, molecular techniques are likely to play a critical role in the diagnosis of orthopaedic infections in general and septic arthritis in particular [18,19]. The newer molecular techniques such as next generation sequencing, because of the rapid decline in DNA sequencing costs, are likely to be even more beneficial in the investigation of patients with orthopaedic infections. These tests will result in a notable decrease in time to diagnose the condition and to isolate the causative organism.

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QUESTION 3: How can superficial surgical site infections (SSIs) be differentiated from deep SSIs (i.e., periprosthetic joint infections (PJIs))?

RECOMMENDATION: There is no single objective clinical test or imaging approach established for the differentiation between a superficial SSI, a deep SSI and a PJI. We recommend that clinical evaluation, workup for infection and early joint aspiration should guide the decision.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

SSIs are infections at the incision site occurring within 30 days after surgery or within one year if implants are left in place [1,2]. The definition commonly used for SSI was specified by the Centers for Disease Control and Prevention (CDC) criteria in 1999 [1]. They are generally categorized into superficial incisional, deep incisional and organ/space SSIs [2,3]. Parvizi et al. proposed a new (2018) definition for PJI (see Question 1, Fig.1) [4]. The new scoring-based definition updated the previous one [5] and is evidence-based with externally validated criteria.

Comparing the aforementioned definitions, CDC criteria for diagnosing SSIs are mainly based on clinical evaluations and histopathology findings, while criteria for diagnosing PJIs also include laboratory results. There is no clinical, laboratory or imaging procedure to reliably allow differentiation between SSIs and PJIs or even between the three different subtypes of SSIs. Furthermore, diagnostic criteria for superficial SSIs, such as tenderness, redness, localized swelling and local heat, have low inter-observer reliability [6]. In the CDC definition, fever above 38° Celsius is considered a clinical sign of a deep incisional SSI [2]. Other wound scoring systems also exist, such as ASEPSIS (Additional treatment, Serous discharge, Erythema, Purulent exudate, Separation of the deep tissues, Isolation of bacteria, and Stay as inpatient prolonged over 14 days). However, neither the CDC definition, nor ASEPSIS differentiate superficial from deep incisional and organ/space SSIs [7]. Additionally, a low-volume knee study demonstrated clinical wound scores (Surgical Wound Aspect Score) with superficial infections having lower scores than deep infection [8]. Despite this finding, the observed difference was not statistically significant [8].

We can assume that PJIs correspond to organ/space SSIs and subsequently, we can attempt to differentiate between superficial SSIs and the organ/space SSIs in a total joint arthroplasty (TJA). A working group of the federal Healthcare Infection Control Practices Advisory Committee completed a comprehensive review of National Healthcare Safety Network (NHSN) SSI definitions in 2011 and 2012. They supported the NHSN adoption of the ICM on PJI's definition of a PJI as the hip and knee arthroplasty "organ/space" SSI [9].

A leaking wound following an arthroplasty can be either the result of a hematoma, seroma, fat necrosis or a sign of deep infection and could also be a risk factor for PJIs (odds ratio (OR) 35.9; 95% confidence interval (CI), 8.3–154.6) [10,11]. Persistent wound drainage may be contaminated and result in a deep infection [12–14]. This knowledge led the 2013 ICM to propose surgical treatment of wound drainage within five days after the index procedure [15]. In a review by Zimmerli, it was proposed that classification of the SSI should guide the selection of the optimal surgical management [16]. An infection occurring within one month of an invasive procedure, such as TJA or arthrocentesis, was classified as an early post-interventional PJI [16]. An acute hematogenous PJI occurs after an uneventful postoperative period with symptoms lasting three weeks or less [16]. Chronic PJI is defined as an infection with symptoms persisting for more than three weeks, or a SSI diagnosed later than one month after implantation [16]. Early post-interventional and acute hematogenous PJIs generally are able to be treated with implant-retaining measures, while chronic PJIs require prosthesis removal due to biofilm formation [16].

A literature review was conducted that revealed no single objective, non-invasive clinical test or imaging approach which can differentiate between a superficial SSI and an early deep PJI. Although several studies address the risk factors for SSI or PJI, none of them differentiated these two conditions [9,17]. We recommend that clinical judgment and early joint aspiration should guide the decision to perform a debridement, antibiotics and implant retention (DAIR) procedure or a superficial debridement. Due to the devastating consequences following PJIs, we recommend that surgeons should have a low threshold for performing a DAIR procedure. Surgeons should also differentiate between stitch abscess, which has only minimal inflammation or discharge from suture points, and superficial and deep surgical site infections. This differentiation can guide the surgeon to perform the needed intervention. Patients in whom the deep space is not involved can be subjected to superficial irrigation and debridement only. In contrast, a DAIR procedure is preferable in patients with deep infections.

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QUESTION 4: How can hip septic arthritis be differentiated from toxic synovitis?

RECOMMENDATION: Currently, there is no single diagnostic test or step that can be performed in order to distinguish a patient with a septic hip from one with toxic synovitis non-invasively. Although algorithms have been created to aid in clinical decision making, there is not enough evidence to support their generalization across all populations, therefore, more research still needs to be conducted before they can be fully validated. Clinical reasoning, evaluation and judgment should still be the standard for which physicians make the distinction between these pathologies as they care for their patients.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Differentiating between a septic hip and toxic synovitis is a balance between the potential morbidity and complications of an undiagnosed, infected hip and unnecessary invasive procedures when conservative management would have sufficed. Clinically, there is major overlap in the presentations of hip septic arthritis and toxic synovitis, and no single variable or laboratory result can sufficiently distinguish the two [1,2]. In fact, laboratory values can all be within normal limits even when hip septic arthritis is confirmed [3,4]. While toxic synovitis is transient, the natural history of an undiagnosed and untreated septic hip can lead to multiple devastating sequelae, such as cartilage damage, osteomyelitis, osteonecrosis and sepsis [5]. Multiple studies have attempted to identify and simplify the diagnostic procedure in order to better guide clinical decision making and treatment.

Although there is no one differentiating factor that can be statistically quantified between hip septic arthritis patients and those with toxic synovitis, Kocher et al. created a clinical algorithm based on four predictive variables [1,5]. These variables include the inability or refusal to bear weight, history of a fever (defined as an oral temperature >38.5˚C), a serum white blood cell (WBC) count greater than 12,000 cells per cubic millimeter (cells/mm3) and an erythrocyte sedimentation rate (ESR) greater than 40 millimeters per hour (mm/hour) [1]. This was carried out retrospectively and then validated later with a prospective study at the same institution [6]. Their results showed a predictive rate of <0.2% and 2.0% without any predictors and up to 99 and 93% when all four predictors were present, in the retrospective and validation study respectively [1,6].

Similar retrospective studies were also carried out at other institutions and included additional diagnostic variables such as C-reactive protein (CRP) and radiographic findings [5,7,8]. Caird et al. found that CRP was a stronger predictor than ESR and in fact was the second strongest predictor behind oral temperature [5]. However, aside from the validation study performed by Kocher et al. at the same institution, the results of that initial predictive model were not reproducible in all populations to the same 99% predictive rate originally described [4].

Another limitation to the current available data lies in the study designs and the statistical analyses used [9]. A systematic review of the literature found that the patient populations did not differ enough to warrant the variance seen in separate studies [9]. The sample sizes of the studies themselves were called into question and even addressed as a weakness in multiple other studies when analyzing the contrast among the studies [5,8–10].

The variability in evidence shows that currently there is no definitive means of distinguishing hip septic arthritis and toxic synovitis non-invasively. Clinicians must continue to use discerning judgment when assessing patients with potentially infected hips through the use of algorithms, imaging and laboratory studies.

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QUESTION 5: What clinical findings (e.g., fever, erythema, reduced range of motion) are most sensitive and specific for the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: A painful prosthetic joint is the most sensitive, but least specific clinical finding in PJIs. Signs of deep tissue involvement (i.e., sinus tract, purulence, abscess and extensive necrosis) are the most specific signs. It is important to note that clinical findings differ notably based on the type of joint involved (hip or knee), as well as to the timing and presentation of PJIs (i.e., early postoperative, acute hematogenous and chronic).

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Clinical findings are evident from the first patient encounter and can be immensely helpful in assessing the pretest probability of a diagnosis, as well as the subsequent interpretation of tests ordered. Published work reporting clinical findings in PJIs are retrospective cohort studies including only infected patients with PJIs without a comparative aseptic cohort. Moreover, they report the findings of hips and knees, chronic and acute infections all together. As a consequence, clinical findings currently play a limited role in the established diagnostic guidelines for PJIs.

We conducted a systematic review to evaluate the main clinical findings associated with PJIs and their diagnostic accuracy. Of 1,028 potentially relevant citations, 38 articles (4,467 PJIs) were included in the present review.

Pain

Pain is the most common symptom in acute and chronic PJIs. This finding by itself justifies further evaluation to rule out a PJI, mainly during the first five postoperative years, when the occurrence of aseptic loosening is less frequent. While its frequency and intensity are higher in acute conditions, pain may be the most prevalent or even the only symptom of late infections, especially in cases of low virulence chronic PJIs. In early postoperative PJIs, the clinical features associated with the recovery process from the surgical trauma may mask the manifestation of pain caused by an infectious condition.

Fever

Fevers are a specific, but inconsistent, finding that are markedly influenced by time from surgery. While frequent during acute hematogenous infections (75.5%), the incidence of fever for early postoperative and late chronic infections, is much lower (32.5 and 14.0%, respectively). It should be emphasized that fever, without an actual infectious condition elsewhere in the body, is a common finding during the first five postoperative days, as part of the physiological recovery from a total hip or knee arthroplasty [1].

Periarticular inflammation (i.e., effusion/swelling, warmth and erythema)

Periarticular inflammation findings are specific for PJIs, but should be considered in the context of the particular joint involved (hip or knee) and the timing from surgery. As a superficial joint, the knee is more suitable for the early recognition of inflammatory signs and, or symptoms. Comparing the incidence of periarticular inflammation between infected total knee arthroplasty (TKA) and total hip arthroplasty (THA), Zajons et al. [2] found rates of 50 and 14% for warmth and 75 and 29% for effusions, respectively. It should be noted, however, that the warmth around the knee might remain elevated even in the condition of uneventful recovery after TKA [3]. Time from surgery also has a major impact on these findings; chronic PJIs more frequently present without periarticular inflammation compared to acute PJIs and pain may be the only clue for infection in these patients.

Superficial disturbances (i.e., delayed healing, non-purulent wound drainage and superficial dehiscence)

Superficial disturbances, although sometimes described as signs and symptoms of PJIs, should initially be seen as surgical wound healing disturbances or manifestations of superficial surgical site infections, therefore, not a diagnostic finding, but a risk factor for deep infections. Thus, closer follow-up and early intervention should be performed, as these features may accompany PJIs in up to 44% of cases of confirmed early postoperative infections [4–8].

Deep involvement (i.e., sinus tract, purulence, abscess and extensive necrosis)

Deep involvement presents the highest specificity of all clinical findings associated with PJIs (i.e., specificity between 97% and 100%, positive predictive value of 100% and accuracy of 84.3%). Thus, when present, they justify the condition of major criteria for the diagnosis of PJIs [9].

Joint dysfunction (i.e., stiffness and reduced range of motion)

Joint dysfunctions are underreported and descriptions differ widely. Tande et al. [10] reported a sensitivity of 20.5% (95% confidence interval (CI), 9.3 – 36.5) and a specificity of 99.0% (95% CI, 94.5 – 100.0) in a sample of 39 acute hematogenous PJIs compared with 100 non-infected controls. The incidence of joint dysfunction in chronic PJIs in a study by Jacobs et al. [11] reached 41.7% (25 of 60 PJIs). Tseng et al. [12] found evidence of joint dysfunction in 37.3% (22 of 59 PJIs). Notably these studies did not specify TKA from THA. Interestingly, when comparing 172 THA with 148 TKA PJIs, Zajons et al. [2] found

an incidence of joint dysfunction of 74% (128 of 172) in the knees compared to 85% (126 of 148) in the hips.

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QUESTION 6: Should intraoperative purulence be considered as a definitive sign of a periprosthetic joint infection (PJI)?

RECOMMENDATION: Intraoperative purulence should not be considered a definitive sign of a PJI. The definition of purulence is subjective and is neither a sensitive, nor specific, diagnostic marker of a PJI. A validated, objective definition for purulence due to infection is required to set purulence as a diagnostic criterion for PJIs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 75%, Disagree: 22%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Purulence, defined as the presence of pus, has conventionally been considered a definitive sign of PJI and many studies have used intraoperative purulence as a single criterion to diagnose PJIs [1–4]. The Infectious Diseases Society of America (IDSA) in a Clinical Practice Guidelines for diagnosis and management of PJI, indicates that the presence of purulence without another known etiology surrounding the prosthesis is a definitive evidence of PJI (B-III) [5]. However, considering purulence around the implant as a definitive sign of infection seems to have several drawbacks.

First of all, the determination of purulence is based on the subjective interpretation of the surgeon. Although most surgeons might agree on frank pus, they would have different thresholds for considering cloudy or turbid fluid as purulence. Therefore, the definition of purulence is subjective and assessment and classification of what constitutes purulence are based on surgeons' training, experience and other factors. Failure to use objective criteria to diagnose PJIs has been shown to substantially increase the reported infection rates [6,7].

Secondly, the presence of purulent-appearing or turbid synovial fluid has been reported in both non-infected native and prosthetic joints [8–12]. Turbid, yellowish-white fluid may represent the neutrophil-rich liquid that develops as part of an inflammatory reaction in response to an infection [13], but it may also be seen in non-infectious problems such as crystalline deposition diseases [14,15]. Although contemporary biomaterials are relatively inert, they may still release particles that provoke an inflammatory reaction in some patients [16]. In addition, purulence can exist in patients with failure of metal-on-metal (MoM) bearing surfaces [8–10] or failure due to corrosion at the trunnion of the femoral stem [11], but that does not represent a PJI. Moreover, concomitant infection and failed MoM arthroplasty have also been reported with indistinguishable appearance of the periprosthetic fluid or tissue from non- infected failed MoM implants [17,18].

Thirdly, it was shown that purulence had an acceptable sensitivity of 0.82 and PPV of 0.91 but the specificity and NPV were exceedingly low (0.32 and 0.17, respectively). The sensitivity of purulence was significantly higher in acute hematogenous and late PJIs (0.92 and 0.89, respectively), compared with early postoperative PJIs (0.66) [19], but it is still low to be a definitive sign of PJIs.

Fourth, in the early postoperative period, the synovial fluid is usually blood-contaminated and evaluation of purulence in this time period is very difficult [19].

Fifth, studies showed that there is no correlation between the intensity of systemic inflammatory response and the presence of purulence in the affected joint. Alijanpour et al. [19] showed no correlation between erythrocyte sedimentation rate and C-reactive protein levels and the percentage of synovial neutrophils and the presence of purulence in their series of 467 patients. However, they showed an association between the mean number of synovial neutrophil count, which is concordant with the concept that puru-

lence represents a local inflammatory reaction consisting of a high synovial white blood cell count.

Therefore, in the absence of an objective definition, it is difficult to consider purulence as a simple dichotomous variable. Subjective opinion of the surgeon regarding periprosthetic fluid can vary based on their clinical impression or concerns regarding the consequences of misdiagnosing PJIs. Moreover, PJI has a serious impact on patients' health and quality of life because patients may be subjected to additional surgical procedures and long-term antibiotic treatment. Therefore, surgeons should be cautious in applying subjective criteria for ruling in or ruling out PJIs in suspected patients.

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QUESTION 7: Is aseptic loosening (AL) associated with an undiagnosed periprosthetic joint infections (PJIs)?

RECOMMENDATION: Some percentage of AL is due to culture-negative infection, since up to 10% of culture-negative cases contain bacteria when screened by molecular methods. Whether this correlates to an undiagnosed infection causing AL remains unclear. Understanding this issue is limited by the ability of bacterial culture to function as an effective gold standard for detecting infection. The role of molecular techniques such as next generation sequencing in this setting needs to be explored.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Loosening is one of the most common indications for total joint arthroplasty revision. Differentiating between PJI and AL is important in determining appropriate treatment. Loosening is considered aseptic when the radiographic or clinical findings associated with loosening are present in the absence of clinical or laboratory evidence of infection. Radiographic determination of loosening has an excellent specificity and positive predictive value, however, a poor sensitivity and negative predicative value, and thus should not be used to exclude loosening [1].

There is the possibility that microorganisms live on or around implants without signs or symptoms of infection, which can lead to AL. Several prospective and retrospective studies have supported that at least a fraction of cases with AL have been associated with higher rates of bacterial growth. The reported prevalence of unexpected positive cultures (UPC) in presumed aseptic revision arthroplasty varies from 5.9 to 23.9% [2–14]. This major variation might be due to small sample size, different culturing protocols (detection of bacteriologic 16S ribosomal RNA by polymerase chain reaction, sonication fluid cultures and conventional techniques of fluid and soft tissue cultures), laboratory contamination rates, as well as the heterogeneity of patients included in each study (i.e., revisions for isolated polyethylene wear, dislocation, fracture and implant loosening) [2,5]. Kempthorne et al. reported a case-control prospective study comparing AL patients (cases) and patients undergoing revision surgery for other causes (control) with a positive culture rate of 15% [2].

Some authors have related early AL to hidden PJIs [3,7,11]. Ribera et al. and Fernandez-Sampedro et al. have observed a correlation between microbiology and prosthesis-age, which supports the possibility of early loosening being caused by hidden PJIs [3,11]. Among the studies reported, there is no consensus about the prognostic impact of UPC. Some authors have shown that even a single positive intraoperative culture has been correlated to prosthetic joint failure, especially with early loosening [11,12]. On the other hand, Portillo et al. have found that the growth of low-virulence organisms in revisions for apparent AL is not associated with early prosthesis failure [8].

While traditional laboratory analysis to evaluate for infection consists of intraoperative culture of periprosthetic tissue or fluids, it has been well-established that microbial culture is an imperfect means of detecting bacteria, as culture has been shown to fail to detect bacteria in as many as 15% of clinically apparent infectious cases [15]. The increasing utilization of molecular methods in recent years has increased the incidence of bacterial detection in cases of AL. One study of 74 culture negative aseptic implants revealed the presence of bacteria in 9 (12%) after screening with polymerase chain reaction (PCR) assays [16].

The discrepancy between traditional culture methods and culture-independent molecular methods to detect bacterial infection in implants has been discussed extensively in the literature [17]. A number of proposed theories have been put forward to explain the absence of cultured bacteria in clinically infected cases, including the effects of prophylactic antibiotic treatment, growth behavior of biofilms and insufficient growth time to detect orthopaedic-specific pathogens. Regardless of the reason, detection via culture appears to be an inadequately sensitive diagnostic tool for periprosthetic joint infections.

A consistent limitation of studies that compare molecular techniques to culture is a failure to perform complete (deoxyribonucleic acid) DNA sequencing. Without this additional information, confirmation and agreement cannot be made between samples that are both culture and PCR-positive. Additionally, the etiology of culture negative and PCR-positive samples cannot be explored. Studies that have conducted full DNA sequencing have found significant discrepancies between the predominant species in culture versus those found via PCR analysis and the classic bacterial species that would be expected in PJIs [16]. The role of contamination in molecular methods also remains ill-defined. A carefully conducted study directly addressing this question found no significant difference in culture and 16S rRNA PCR of explanted implants [18].

An alternative theory to explain the phenomenon of culture-negative and PCR-positive clinically infected cases is the role of endotoxin. The detection limits for endotoxin are comparable to the stimulatory threshold, possibly resulting in unrecognized endotoxin [19]. Endotoxin alone replicates the effect of aseptic loosening [20] and can also adhere to titanium particles and implant surfaces [21]. In cases where bacteria are truly eradicated, cellular debris may create a false positive PCR, and residual endotoxin may initiate a local inflammatory response, resulting in culture negative loosening [22].

It is apparent that advanced modern molecular techniques detect bacteria in aseptic joints at a greater rate and with greater diversity than traditional microbial cultures. It is likely that a PJI is present in a greater number of cases with implant loosening than previously suspected. More detailed studies are required to determine the true incidence of loosening due to infection and the exact pathogenic process that may differentiate culture and PCR-positive infections from culture-negative, but PCR-positive infections.

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QUESTION 8: Can periprosthetic joint infection (PJI) be assigned a high- or low-grade infection? If so, what is the definition of each grade?

RECOMMENDATION: Yes, PJI can be scored and assigned an "infection grade." At this juncture, we recommend using the McPherson schema as a starting point for grading PJIs, as this system demonstrates outcomes correlating with worsening host and limb scores. We suggest this schema (or a modified version) as a starting point until an international workgroup establishes a codified staging system.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 74%, Disagree: 12%, Abstain: 14% (Super Majority, Strong Consensus)

RATIONALE

Infection severity in PJI depends upon multiple factors. These include: infection duration (i.e., acute, acute hematogenous or chronic), the ability for the patient (i.e., host) to combat the infection, the quality of the tissues around the infected joint, the ability for the limb to heal and the "aggressiveness" of the organism.

The duration of infection relates more to the presence of biofilm. Acute infections are essentially non-biofilm-related infections. They characteristically present with abrupt onset and manifest with rapidly increasing pain, displaying overt signs of infection and, not infrequently, developing systemic effects and sometimes even septic shock. Acute PJIs can be successfully treated with early radical debridement surgery. The success of implant retention long-term depends on many factors including early versus late intervention, host comorbidities and local wound health.

In contrast, a chronic PJI involves biofilm formation. This is important because the clinical manifestation of a PJI developed from a biofilm is markedly different from an acute (non-biofilm) infection. In a biofilm-related infection, bacteria and/or fungi adhere to the implant, colonize and expand in size. Once the colony reaches a genetically predetermined size, the colony undergoes a metamorphosis into a biofilm colony (via phenotypic expression). The microbial biofilm then encapsulates the implant system, erodes into the surrounding bone and eventually enters the medullary canals. Furthermore, biofilm colonies are highly resistant to antibiotics, whereby they become 1,500 to 10,000 times more resistant to typical minimum inhibitory concentration (MIC) of antibiotics.

The clinical presentation of a biofilm infection mirrors the progression of the advancing biofilm. This includes gradually increasing pain and periarticular swelling and warmth on examination. Functional limitations result when implant stability is compromised by marginal erosive osteomyelitis. Biofilm bacteria erode into the periarticular soft tissues, creating multiple loculated abscesses destroying vital joint ligaments, tendons and muscle. Not infrequently, a burrowing abscess will erode to the skin surface creating a chronic sinus tract. The time sequence for developing a mature biofilm is variable, but can develop as soon as a few days after the onset of infection in a patient with a joint arthroplasty in place. The rate of biofilm development depends on host immunity and limb health (i.e., local wound health). Characteristically, biofilm infections are considered "indolent" infections, as patients are not systemically ill. This is because endotoxic or exotoxic responses are not manifested with biofilm infections. A biofilm PJI must be treated with implant removal combined with a radical "tumoresque" removal of adjacent soft tissues and bone. This can be accomplished either with a single or two-stage exchange. The choice of single- versus two-stage exchange again hinges upon host and limb health, which can be scored and rated. In the overall totality of PJIs, biofilm PJIs cause vastly more internal damage to the musculoskeletal system than acute infections. Thus, many physicians and surgeons consider a long-standing chronic biofilm infection to be the more severe infection.

The human immune system plays the most critical role as it relates to infection containment and eradication, for both acute and chronic infections. As a general rule, the weaker the human host, the weaker the immune system and, thus, the greater the severity of infection/conditions. There are numerous medical conditions, medications and treatments that can suppress immune system function and alter the course of a PJI [1]. These conditions that have been shown to increase infection risk are well enumerated in the literature over the last four decades.

Grading Schemes

Several schemata for classifying the human host and PJI have been introduced, beginning in the late 1990's. Several authors, including Tsukayama, McPherson, Hanssen and Wimmer, have proposed staging systems for PJIs [2–7]. These have been based on retrospective studies that rate human host quality (i.e., host grade), correlating host grade with worsening outcomes. McPherson et al. has correlated worse outcomes with declining host grade and limb score in both total hip arthroplasties (THAs) and total knee arthroplasties (TKAs) [4,5]. This has been confirmed by Kaplan Meier survival analysis in a recent retrospective review by Bryan et al. [8]. Recently, another study of second-stage THA for chronic infection correlated infection recurrence directly to a compromised host grade [9]. Generally speaking, many infection-specific societies, such as the European Bone and Joint Infection Society (EBJIS), are adopting the staging of host immunity along with limb scores as a means to compare clinical outcomes. In this manner, future treatments for PJIs can be tailored, similar to cancer therapy, based upon an agreed staging system.

Limb tissue health also plays an important factor in infection treatment. Poor tissue health correlates with poor healing and infection persistence. Many factors have been described that limit healing, including arterial and venous insufficiency, sensory and motor neuropathies, soft tissue loss and tissue quality (e.g., irradiation, burns and/or multiple incisions). A poor "limb score" should correlate with reduced outcomes scores, however measured. There are quantifiable parameters with retrospective data supporting this concept. McPherson's schema is thus far the only system that rates limb health and has shown a correlation of impaired limb scores with worsening functional outcomes [4,5,9].

Aggressiveness of an organism is hard to quantify and qualify. The organisms more likely to form a biofilm and persist have multiple techniques to adhere to an implant surface and form a

biofilm. In contrast, organisms that present with acute infections frequently produce toxins that result in a systemic toxicity and eventually shock. Vasso defined a low-grade infection as one that is not causing systemic illness [10]. Symptoms are sometimes ill-defined. Lab serologies may be slightly elevated and cultures can be difficult to grow. When an organism is isolated it is often a low-virulent organism, such as *Staphylococcus epidermidis* or *Cutibacterium acnes* (formerly *Propionibacterium acnes*). In contrast, a high-grade infection has not been as well-established in the literature [11]. One can deduce that it would be caused by an organism causing systemic illness/sepsis or acting aggressively at the site (i.e., severe pain, swelling, drainage, etc.). Currently, there is no method of qualifying these parameters. Medical advancements, such as 3rd and 4th generation deoxyribonucleic acid (DNA) sequencing, will help make it a possibility to identify genetic sequences that correlate with "organism aggressiveness" and poor outcomes. Only then will we be able to truly "rate" the severity of an invading organism.

Conclusions

In summary, there is substantive data that supports the concept of grading or rating a PJI. The data that supports grading PJI severity is retrospective in nature. There is not yet an international codified system that multiple investigators have agreed upon. Our recommendation is to gather an international workgroup to establish a PJI grading system, utilizing current tools and data available. The system of grading should be reviewed and upgraded every five years, as newer diagnostic tools and outcome data become available. For now, the McPherson schema has taken hold and is used in presentations worldwide over the past three to five years. We suggest using this system (or a modified version) as a starting point until an international workgroup establishes a codified staging system upon which the majority agrees.

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2.2. DIAGNOSIS: ALGORITHM

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QUESTION 1: Do you agree with the American Academy of Orthopaedic Surgeons (AAOS) algorithm for the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Yes. However, since the introduction of the AAOS algorithm for diagnosis of PJIs, numerous new tests and diagnostic modalities have become available. The proposed evidence-based and validated algorithm includes the guidelines from AAOS and the 2013 International Consensus Meeting (ICM) on PJIs. A stepwise algorithm first using serological markers followed by more specific and invasive tests continues to be recommended.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 73%, Disagree: 23%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

The guidelines for the diagnosis of PJIs introduced by the AAOS provided useful parameters for clinicians and a framework for diagnosing PJIs [1,2]. These guidelines have been widely adopted and were endorsed at the last ICM on PJIs in 2013 with slight modification [3]. While the existing algorithms are widely accepted, they are not completely evidence-based and have not been validated. Furthermore, several new synovial [4], serum and molecular biomarkers [5–10] have been introduced in recent years, which have increased confusion as many surgeons are unsure how to incorporate these tests into their practice and into the previously established guidelines.

With the introduction of new diagnostic tests and the need for validation of the guidelines, we have been prompted to expand on the prior guidelines and to develop an evidence-based, validated diagnostic algorithm. A multi-institutional study was performed by members of this workgroup, to generate a stepwise approach using random forest and multivariate regression analyses to generate relative weights and to determine which variables should be included

in each step. Ultimately, the algorithm shares many similarities to the previous algorithm as serological testing should be performed first, followed by more invasive tests. This stepwise approach of serological markers prior to joint aspiration has been demonstrated to be the most cost-efficient method of diagnosing PJIs using a multicriteria decision analysis in prior studies [11].

The first step in evaluating for a PJI should include serum testing for C-reactive protein, D-dimer and erythrocyte sedimentation rate. If at least one is elevated, or if there is a high clinical suspicion, clinicians should proceed with synovial fluid testing including a synovial fluid white blood-cell count with differential and leukocyte esterase testing. Intraoperative findings including purulence, histology, next generation sequencing (NGS) or a single positive culture can aid in cases where the diagnosis has not been conclusively ruled in or out prior to revision surgery, or when the aspiration does not yield fluid for analysis (a dry tap). The proposed algorithm was formally validated on a separate cohort of patients and demonstrated a high overall sensitivity (96.9%, 95% confidence interval (CI): 93.8-98.8) and specificity (99.5%, 95% CI: 97.2-100).

In the patient with a painful total joint arthroplasty, it is important to always consider infection. Initially, the first step considers patient risk factors, clinical findings and serum markers; the latter two of which have high sensitivity, but not necessarily high specificity in order to minimize false-negatives. In the multicenter study, approximately 13% of PJIs could be diagnosed with the first step based on a positive sinus tract. It is important to consider clinical suspicion and patient risk factors, (i.e., pretest probability), to optimize sensitivity as serum testing alone is negative in approximately 2.5% of patients who have a PJI [12]. The next step in the investigation of PJIs requires synovial fluid testing which has greater sensitivity and specificity, but is more invasive. The majority of PJIs will be identified following joint aspiration and synovial fluid analysis (approximately 65%). If a diagnosis of PJI cannot be confirmed or excluded at this point, intraoperative findings should be used and approximately 17% of PJIs will be diagnosed after incorporating intraoperative findings including culture, histology, operative appearance and NGS.

It is important to note that it is possible that the diagnosis of PJI may not be made even after reaching the third stage or may be inconclusive after obtaining synovial tests. These patients are often encountered in clinical practice and represent a real diagnostic challenge. Future research and novel tests are certainly needed in this patient population to reduce the gray area in these borderline patients without overt infection. Furthermore, it is important to note that the proposed algorithm and the definition of PJI may be inaccurate and require a modification in the tests utilized for the following conditions: adverse local tissue reactions, crystalline deposition arthropathies, inflammatory arthroplasty flares and infections with slow growing organisms, such as *Cutibacterium acnes* (formerly *Propionibacterium acnes*). Nevertheless, we hope that the introduction of this evidence-based and validated algorithm may simplify a very challenging process and account for recent advancements in the diagnosis of PJIs.

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QUESTION 2: Are there any contraindications to knee or hip aspiration prior to revision surgery?

RECOMMENDATION: There are no clearly identified contraindications to aspiration of the knee or hip joint performed as part of the patient workup for infection.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Aspiration of a joint is one of the most important aspects of the workup of a patient suspected of having an infected joint. There are numerous studies that have demonstrated the utility of joint aspiration in aiding diagnosis of periprosthetic joint infections (PJIs). In fact, joint aspiration is one of the initial steps in the workup of a patient for diagnosis of PJI, which is reflected in the algorithm

that is proposed by the International Consensus Meeting (ICM) and presented elsewhere in this document.

The question here is not, however, regarding the utility of joint aspiration in the diagnosis of PJIs, but is regarding possible contraindications for joint aspiration. To our knowledge, there is no publication that specifically addresses this question. In clinical practice, there are a few situations that may compel an orthopaedic surgeon or other physicians to avoid aspiration of the joint. One situation is the presence of cellulitis around a joint that is being investigated, with the concern here being that placing a needle through a potentially infected tissue might transfer bacteria into the deeper space of the joint and result in infection. There are no studies that specifically address issues of cellulitis or skin problems overlying the site of aspiration.

The other situation when physicians may refrain from aspiration of a joint is when the patient is on an anticoagulant. There are several studies that discuss the issue of joint injection or aspiration for patients on concomitant anticoagulation medications. Most of the studies address injections and not aspirations, or have far fewer patients undergoing aspiration than injection. Of the studies that are available, there are several low to moderate quality investigations that discuss patients on anticoagulation during an injection or aspiration. None of these studies have found a statistically significant increase in complications including bleeding or infection related to the procedure.

Yui et al. performed a retrospective review of patients on direct oral anticoagulants (DOACs) undergoing arthrocentesis or joint injection [1]. There were 1,050 procedures reviewed with no major bleeding complications reported. Ahmed et al. conducted a retrospective review of clinical records of patients who were on therapeutic anticoagulation, comparing arthrocentesis or joint injection in patients who had an international normalized ratio (INR) of >2.0 (456 procedures) to those with INR <2.0 (184 procedures) [2]. The authors found only one major bleeding complication and one late infection in the group with an INR > 2.0 and no statistically significant differences between the two groups. It is important to note that many of the patients in both of these studies were also on antiplatelet agents, but subgroup analysis was not performed. Other small, low quality studies have shown no significant risk of complications [3][4]. A recent review of literature of bleeding risks associated with musculoskeletal procedures recommends that anticoagulation agents such as aspirin, clopidogrel, warfarin and low-molecular-weight heparin (LMWH) should not be discontinued in patients undergoing arthrocentesis and/or joint injections [5]. The conclusions of the latter study were based on the review of the available literature. Although high level studies are lacking, there is some support from retrospective studies for performing joint aspiration in patients who are on anticoagulation.

There is no high-level publication regarding the issue of aspirating a joint through skin affected by cellulitis or other skin lesions, such as psoriasis. The available studies are all expert opinions [6]. In the absence of concrete evidence, we feel that joint aspiration performed as part of workup for PJI is a critical diagnostic step and should be performed even in the presence of cellulitis or other skin lesions. Whenever possible, however, the aspiration should be performed through an area that is least affected. Consideration should also be given to postponing the aspiration in patients with stable and chronic issues until any skin lesions have resolved. The decision to proceed with aspiration in patients with skin lesions around the affected joint needs to be individualized and weighed against the theoretical risk of seeding the joint with bacteria from the overlying affected skin.

Another situation that may create issues regarding aspiration of a joint is in patients with bacteremia. It is hypothesized that traumatic arthrocentesis can theoretically introduce infected blood into the sterile joint. There are no human studies related to this subject matter and no studies have specifically evaluated the risk of PJIs in this situation. Olney et al. investigated the risk of performing a joint aspiration in the setting of bacteremia using a rabbit model and found that 30% of animals developed septic arthritis if blood drawn from an animal with bacteremia was injected into the joint [7]. Thus, one can extrapolate that performing a traumatic arthrocentesis in patients with positive blood cultures may potentially result in seeding of the aspirated joint and subsequent infection. This theoretical risk should also be individualized and weighed in the context of benefits versus risks of joint aspiration.

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QUESTION 3: In the setting of a dry tap, should lavage with a fluid be performed?

RECOMMENDATION: We recommend against injection of normal saline or other fluids into a joint that did not yield any synovial fluid (dry tap) and is being investigated for a periprosthetic joint infection (PJI); except in certain circumstances (e.g., a dedicated radiologist performing aspirate in a sterile fashion).

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 83%, Disagree: 14%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Joint aspiration is a valuable investigation for the diagnosis of a PJI. In addition to providing information regarding synovial white blood cell (WBC) count, neutrophil differential and biomarkers, it can identify the infecting organism and antibiotic susceptibility [1]. Furthermore, it can guide surgical and antibiotic treatment strategies, such as the choice of appropriate antibiotics for parenteral administration, use of local antibiotics or addition of antibiotics to cement [2]. Aspirated synovial fluid is usually sent for a synovial fluid WBC count, neutrophil differential and processed for isolation of aerobic and anaerobic microorganisms [3]. Given the ability to get these three data points from one intervention, arthrocentesis remains one of the best single maneuvers physicians can perform to rule in or rule out the diagnosis of PJI [4].

A prospective study of 207 revision total hip arthroplasties (THAs) found that hip aspiration had a sensitivity of 0.86 and specificity of 0.94 for diagnosis of PJIs [5]. Moreover, the authors proposed a selective role for aspiration. They concluded that hip aspiration should be limited to confirming clinical suspicion of infection or as an adjuvant investigation when inflammatory markers were falsely elevated secondary to other disorders. Additionally, Barrack et al. performed a retrospective review of 270 hips with routine preoperative hip aspiration, reporting a sensitivity and specificity of 0.50 and 0.88 for the first aspiration, respectively, and a false-positive rate of 13% [6].

However, a dry tap of prosthetic joints is not infrequent and can be disappointing in the setting of an evaluation for PJIs. Historically, injection of sterile saline into the joint followed by re-aspiration has been described as a method to overcome this problem. To date, there are no high-quality studies published supporting the diagnostic value of such a method. Additionally, some studies have suggested the subcutaneous tissue infiltration of local anesthetic and intraarticular injection of contrast media should be avoided. This is due to concerns about potential bactericidal and bacteriostatic properties of local anesthetic and contrast media, respectively [7,8]. This preoperative strategy can also dilute microorganism concentration, be unrepresentative of joint fluid and carries a potentially increased risk of causing an infection in an otherwise aseptic arthroplasty. For these reasons, many investigators recommend against lavage of a prosthetic joint that had a dry tap [1,6,9,10].

A few orthopaedic studies consider lavage of the joint and re-aspiration a valid technique to obtain fluid for samples. The sensitivity of this fluid is comparable to the hip aspirations in which good volumes of fluid were aspirated [11–15].

In a retrospective review, Ali et al. [11] investigated 73 potentially infected THA patients, reporting 82% sensitivity, 91% specificity, 74% positive predictive value (PPV), 94% negative predictive value (NPV) and 89% accuracy of preoperative hip aspiration compared with tissue culture for diagnosis of PJI. Of note, 23 (34%) patients had an initial dry tap and were re-aspirated following saline injection resulting in 83% sensitivity, 82% specificity, 63% PPV and 93% NPV. The authors suggest that using saline lavage is reasonable, with comparable sensitivity, but poorer specificity to standard synovial fluid aspirations [11]. However, given the low number of subjects (73 patients), the conclusions of the latter study have limits and cannot be generalized.

Another retrospective study by Somme et al. [12] investigated the use of lavage to aid in the diagnosis of PJIs in 109 patients scheduled for hip revision. Of the 109 aspirates, 23 were gained using lavage and 10 of these patients were correctly diagnosed with infection, with the remaining 13 patients found to not have an infection. Furthermore, this study used lavage regardless of whether a pre-lavage specimen was obtained in 107 aspirates. No patients with a positive post-lavage specimen had a negative pre-lavage specimen. The authors noted that there is value in using saline lavage in dry taps.

Additional early studies demonstrated inconclusive results with respect to lavage following a dry tap. Roberts et al. [13] utilized saline lavage when encountering a dry tap in the aspiration of patients awaiting revision THA with 38 (49%) dry tap aspirates, 5 of which were shown to be infected at the time of surgery. Of these, three had grown organisms from the saline washings and two were false-negatives. In a retrospective review of 71 THA revisions, Mulcahy et al. [14] used saline lavage in three infected patients with dry taps, however, no organisms were cultured from the saline washings.

More recently, Newman et al. [16] reviewed the WBC count and polymorphonuclear (PMN) percentage in infected and non-infected hips being treated with antibiotic cement spacers, comparing aspiration with or without saline lavage. Aspirations performed without lavage yielded a positive culture in 84% [95% confidence interval (CI), 81%-90%]; but in the saline lavage group, positive cultures were found in 76% (95% CI, 76%-86%). There was no difference in the WBC count or PMN percentage in infected versus non-infected hips when using saline lavage. Therefore, saline lavage was not recommended for the diagnosis of persistent infection in this particular cohort of patients. Moreover, a recently published algorithm-based approach for the diagnosis of PJI does not recommend lavage of the joint with sterile saline in order to obtain samples [1]. In contrast, Partridge et al. [17] performed a retrospective review of 580 hip and knee aspirations and concluded that aspiration with lavage following a dry tap provided accurate diagnostic information and yielded similar sensitivities and specificities to direct aspirations.

Given the paucity of evidence, there appears to be little benefit in attempting lavage of a joint when a dry tap is encountered. Importantly, there appears to be a risk of false-negative results when using this technique. This practice may be best justified if there is a special musculoskeletal imaging specialist who is able to perform the lavage and aspiration with great accuracy. In the absence of such specialist, repeat aspirations or alternative diagnostic methods should be employed in the event of a dry tap. In the absence of consistent evidence, further prospective studies with larger cohorts are required.

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QUESTION 4: In patients with multiple arthroplasties in place who have developed a periprosthetic infection (PJI) of one joint, should other joints be investigated for PJIs also?

RECOMMENDATION: We recommend that when a patient develops a PJI in one joint, the other total joint arthroplasties (TJAs) should be examined clinically and if suspicion for PJI remains, or the patient is immunocompromised, then other joints should be aspirated.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Up to 45% of patients undergoing primary TJA due to idiopathic osteoarthritis require at least one additional, distant, TJA [1]. Due to increasing numbers of TJAs performed every year and the continuous aging population, patients with multiple arthroplasties are expected to increase. Furthermore, mortality rates after revision for PJIs are estimated to be significantly higher than mortality rates after aseptic revisions [2]. This highlights the importance in determining the infection status of other joints in patients with a PJI.

A frequent concern has always been the presence of distant joint PJIs secondary to possible hematogenous seeding [3–14]. Murray et al. were the first to define metachronous, different joint PJIs [12]. They estimated that the risk of failure of a second, prosthetic joint, already in place, when an initial PJI develops, could be as high as 18%. A limited number of studies have been published evaluating the risk of PJIs in patients with multiple arthroplasties [13–17]. Luessenhop et al. presented a similar incidence of 19% of other joint infections among 145 patients who had more than one joint in place at initial PJI [13]. They also identified rheumatoid arthritis as a risk factor among these patients. Furthermore, in a cohort of 55 patients, Jafari et al. showed a 20% incidence of distant subsequent infection at a mean of two years [14]. They also evaluated that the type of organism of the subsequent infection was found to be the same in 36% of the patients. Abblitt et al., in a more recent study, evaluated 76 patients with multiple joints replaced and estimated the rate of subsequent infection to be lower, at 8.3% [15]. This study also emphasized the role of bacteremia during the first infection in developing a subsequent infection. Haverstock et al. described a 6.3% risk of a subsequent PJI from a total of 206 patients [16]. They identified the same bacteria of the subsequent PJI in only 2.9%. Zeller et al. derived 16 patients with concomitant PJIs, from a cohort of 1,185 with prosthetic hip or knee infections, corresponding to 1.4% of their total PJI population [17].

Studies have been consistent in demonstrating that the risk of developing a PJI in a second prosthetic joint is higher than the base line PJI [12–17]. The estimated risk of second joint PJI ranges from 1.4 to as high as 20%. Rheumatoid arthritis and bacteremia have been identified as possible risk factors for an increased risk of multiple joint infections [13,15]. These published data acknowledge that the other prosthetic joints are at increased risk and raise suspicions whether an ongoing sub-acute infection is present at the time of the initial PJI. However, no study in the literature has evaluated whether at the time of the initial PJI, other arthroplasties should be also investigated.

Nevertheless, investigation of other prosthetic joints should be performed depending on the symptoms of that joint at the time of the other joint PJI. The initial approach should include clinical evaluation. If symptoms are present, initial radiographic evaluation should be performed and in the setting of suspected infection, synovial fluid aspiration should be attempted. Clinical investigation must be undertaken always to identify signs that can raise concern for underlying infection. If aspiration is performed, synovial white blood cell (WBC) count and polymorphonuclear (PMN) % should be requested as they have shown to be highly accurate test modalities [18]. On the contrary, cost-effectiveness of aspirating other joints has also not been investigated; therefore, recommendation in favor or against cannot be made with available data. However, we recommend clinical evaluation of other joints to minimize the risk of failure in the treatment of PJIs.

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QUESTION 5: Are point-of-care (POC) rapid tests for diagnosing periprosthetic joint infections (PJIs) validated and useful?

RECOMMENDATION: Yes, there are several useful POC tests which can be added to the diagnostic workup of PJIs. A number of studies support the usefulness and reliability of the leukocyte esterase (LE) test strip and the alpha-defensin lateral flow test kit. Diagnostic criteria for PJIs should be updated and consider inclusion of these tests.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 73%, Disagree: 21%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

A POC test is defined as a medical diagnostic tool which is used at the time of evaluation of a patient with an immediate result. These are rapid and simple medical tests that can be performed at the bedside. The idea behind a POC test is to provide real-time information upon which the treating physician can act.

After our systematic review, 11 original papers [1–11] and 4 review articles [12–15] assessing the diagnostic value of the LE test strip were included. The pooled data of 2,061 patients extracted from the original papers revealed a sensitivity of 85.7% (95% confidence interval (CI), 65.9 to 90.7%), a specificity of 94.4% (95% CI, 85.3 to 97.7%), a positive predictive value (PPV) of 84.3% (95% CI, 71.5 to 91.7%) and a negative predictive value (NPV) of 94.0% (95% CI, 85.8 to 97.1%).

The first prospective study investigating the utility of the LE strip test in diagnosing PJIs was conducted by Parvizi et al. A total of 108 patients who had painful total knee arthroplasties (TKAs) were investigated and the LE test (with a positive result being ++) had a sensitivity of 80.6% (95% CI, 61.9 to 91.9%), specificity of 100% (95% CI, 94.5 to 100.0%), and PPV of 100% (95% CI, 83.4 to 100.0%). The authors concluded that the LE strip test could be used effectively, by itself or in conjunction with other tests, either as a rapid screening mechanism or for confirmation of a suspected PJI [6].

In a systematic review of Wyatt et al. involving nearly 2,000 patients from five studies, the pooled diagnostic sensitivity and specificity of LE for PJI was 81% (95% CI, 49 to 95%) and 97% (95% CI, 82 to 99%), respectively [15]. Another meta-analysis of eight qualified studies with a total of 1,011 participants showed a higher pooled sensitivity of 90% (95% CI, 76 to 96%) and a similar specificity of 97% (95% CI, 95 to 98%) [14].

The limitation of the LE test is blood contamination interfering with readability of the test result. A recent study confirmed the reliability of the LE strip test by reporting an excellent sensitivity (92.0%) and specificity (93.1%). Furthermore, the latter study confirmed that synovial fluid centrifugation is an effective means of overcoming interference from erythrocytes [5].

After our systematic review, six original papers [16–21] and one review article [22] assessing the diagnostic value of the alpha-defensin lateral-flow test were included. The pooled data of 486 patients showed a sensitivity of 78.5% (95% CI, 64.7 to 94.5%), a specificity of 93.3% (95% CI, 87.0 to 99.6%), a PPV of 87.2% (95% CI, 74.6 to 98.1%) and a NPV of 90.2% (95% CI, 83.7 to 98.2%).

Deirmengian et al. introduced alpha-defensin as a robust synovial biomarker; however, the first studies were published about the laboratory-based enzyme-linked immunosorbent assay (ELISA) test (immuno-assay) [2]. Recent studies showed validated good results of the lateral-flow version of the alpha defensin test being a POC test [16–21]. A level II diagnostic study based on the results of 121 patients revealed a sensitivity and specificity of 97.1 and 96.6%, respectively [17]. The largest series was published by Gehrke et al. as a level I diagnostic study with 195 joints of 191 patients. The overall sensitivity of the alpha-defensin PJI test was 92.1% (95% CI, 83.6 to 97.1%), the specificity was 100% (95% CI, 97.0 to 100%), the PPV was 100% (95% CI, 94.9 to 100%), and the NPV was 95.2% (95% CI, 89.9 to 98.2%). The overall accuracy was 96.9% (95% CI, 93.4 to 98.9%) [18].

In the meta-analysis performed by Suen et al., the pooled sensitivity and specificity of the alpha-defensin lateral flow test was somewhat less appealing, being 77.4% (95% CI, 63.7 to 87.0%) and 91.3% (95% CI, 82.8 to 95.8%), respectively [22]. There is clear evidence that the lateral-flow test has a lower accuracy than the lab-based ELISA immuno-assay [18,22]. The test results may be influenced by metallosis [19] or crystal arthropathy, such as gout [23]. In addition, the

test is somewhat difficult to perform as it involves multiple steps for preparation of the sample.

In a recent meta-analysis about synovial fluid biomarkers alpha-defensin and LE demonstrated high sensitivity for diagnosing PJIs, with alpha-defensin being the best synovial marker. However, other synovial fluid tests like synovial fluid leukocyte count, polymorphonuclear (PMN) %, C-reactive protein (CRP), Interleukein-6 (IL-6) and Interleukin-8 (IL-8) that demonstrate good diagnostic performance can also be used in combination for the diagnosis of PJIs [12]. Molecular diagnostic studies, such as synovial alpha-defensin and LE, may provide rapid, accurate identification of PJIs, even in the setting of concurrent antibiotic administration or systemic inflammatory disease [13].

Additionally, there are a few studies exploring potential technologies which were developed as bed-side tests detecting calprotectin [24,25] or bacterial DNA sequences [26,27] as possible diagnostic tools of the future.

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QUESTION 6: What is the prevalence of culture-negative periprosthetic join infections (CN-PJIs) and what are the diagnostic protocols for further investigating these cases?

RECOMMENDATION: The reported prevalence of CN-PJIs in the hip or knee has ranged from 5-42%. Diagnostic protocols for further investigating these cases include repeat sampling, longer incubation of culture samples, sonication of implants, the use of dithiothreitol (DTT) technology, polymerase chain reaction (PCR) and next generation sequencing (NGS).

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Prosthetic joint arthroplasty is one of the most commonly performed surgical procedures in the field of orthopaedics. Among many complications of prosthetic joint arthroplasty, PJIs are among the most catastrophic [1]. It can develop after 1 to 2% of primary hip arthroplasties and 2 to 3% of primary knee arthroplasties [2,3]. The prevalence of PJIs appears to be on the rise because of numerous reasons, most importantly related to the increasing number of patients receiving arthroplasties. Management of PJIs in general, and CN-PJIs in particular, continues to cause challenges.

The incidence of CN-PJI has been reported to range from 5-42.1% in the literature [4–10]. Klement et al. published a study on patients with PJIs who were diagnosed with the MusculoSkeletal Infection Society (MSIS) major criterion or a combination of MSIS minor criteria, and demonstrated that the incidence of CN-PJI was 0.4% and 45.4%, respectively [11].

CN-PJIs are reported to be associated with older age, smoking, referral from outside institutions, preoperative antibiotic treatment and the presence of postoperative wound drainage [1,4].

Some studies reported that 46% of CN-PJI were caused by fungi, 43% by mycobacteria and 11% by other bacteria such as *Listeria monocytogens*, *Cutbacterium acnes (C. acnes),* Brucella, Coxiella burnetii and others [1].

CN-PJI remains a challenging condition to manage, because of the lack of guidelines or protocols to diagnose and manage these patients in particular with regard to the type of antimicrobials needed for treatment [4]. Because an accurate diagnostic algorithm is not available, most clinicians rely on physical examination, clinical suspicion, laboratory tests and radiological findings to reach the diagnosis of PJI in these cases [1]. Clinical and radiographic evaluations are not always reliable for diagnosing CN-PJI and serum indicators may be inconclusive especially in patients with previous antibiotic administration or those infected with slow-growing organisms. Thus, there has been a growing interest in better diagnostic methods that can isolate the infecting microorganisms associated with implant-related infections.

There are a number of efforts that can be made to improve the yield of culture. Obtaining multiple samples, expeditious transfer of culture samples (especially in blood culture bottles) and prolonged incubation of culture samples are proven to be effective [3,12].

Another strategy to improve isolation of infecting organisms is to subject the retrieved implants to sonication in a sterile fluid. This technique was described a few decades ago and popularized by Trampuz et al. who demonstrated that the culture of sonication fluid had a better yield for isolation of infective organisms of hip and knee PJIs than routine culture [12].

Numerous investigators have described the use of molecular techniques in isolating the infective organism. Perhaps the first molecular technique to be evaluated for isolation of infective organisms in PJI was the polymerase chain reaction (PCR) [13–16]. Tuan et al. continued their efforts to optimize the PCR technology and reported their experience with the use of reverse transcriptase RNA (ribonucleic acid) that aimed to reduce the incidence of false-positive cases [15,16]. Other investigators have shown promising findings with the use of PCR as well. Melendez et al. showed that the PCR accuracy for detecting microorganisms in synovial fluid is 88% and these authors demonstrated that PCR can be used to detect unusual species such as Candida and antibiotic-resistant methicillin-resistant *Staphylococcus aureus* (MRSA) [17]. Bereza et al. was able to isolate bacterial DNA using PCR in 90% of patients [18].

One of the issues related to the use of conventional PCR relates to its extreme sensitivity as it can amplify the DNA of contaminated microorganisms. Because of this issue, PCR has not been used as a first line or a single diagnostic tool in the detection of PJIs [1]. Another issue with the use of conventional PCR is that the type of organisms being sought need to be known to allow for the design of the primer. It is clear that the type of infective organisms is not always known. Thus, a broader approach with the use of multiplex PCR has also been investigated. Jacovides et al. explored the utility of the multiplex PCR using the Ibis Biosciences T5000 biosensor system in a cohort of prospectively collected synovial fluid specimens [19]. In the 23 cases that were considered clinically infected, the PCR panel detected the same pathogen isolated by conventional culture in 17 of 18 cases, and also detected one or more organisms in 4 of the 5 culture-negative cases. In addition, the panel detected organisms in 88% (50 of 57) cases in which revision arthroplasty was performed for a presumed aseptic failure.

Tarabichi et al. first demonstrated the utility of NGS for pathogen detection in PJI with the detection of *Streptococcus canis* in a previously presumed culture-negative case [20]. In a recent report, NGS was demonstrated as a useful adjunct for pathogen detection in 81.8% of culture-negative PJI where intraoperative tissue samples were analyzed [21]. Furthermore, in a series of 86 synovial fluid samples, high concordance with microbiological culture was seen with NGS of synovial fluid alone [22].

Thoendel et al. also showed that metagenomic shotgun sequencing is a powerful tool to identify a wide range of PJI pathogens and may be helpful to diagnose the organism in CN-PJI [23]. Based on their study, metagenomics was able to identify known pathogens in 94.8% of culture-positive PJIs. New potential pathogens were detected in 43.9% (43 of 98) CN-PJIs. Detection of microorganisms in samples from uninfected aseptic failure cases was conversely rare (3.6% of cases).

The analysis of synovial fluid with new biomarkers are currently being studied clinically [3]. The alpha-defensin test shows good results in detecting PJIs [1,3,24,25]. The sensitivity and specificity of the alpha-defensin test is greater than 95% and unlike other biomarkers (i.e., erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), polymorphonuclear (PMN) count) it is not affected by previous antibiotic administration [25–27].

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QUESTION 7: Do patients with adverse local tissue reactions (ALTRs) have a higher incidence of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Yes. Patients with ALTRs appear to have a higher incidence of PJIs.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

The diagnosis of PJI can be extremely challenging in patients with a metal-on-metal (MoM) bearings or modular junction-induced ALTRs. The clinical presentation of ALTR may mimic that of PJI and both serum and serologic markers may be elevated in both conditions. Intraoperative findings may include extensive soft tissue necrosis, macrophage foreign body response, perivascular lymphoid infiltrate and even grossly appearing purulent fluid [1–3]. Preliminary research suggests that MoM wear and corrosion particles may alter the periprosthetic environment, therefore increasing the risk of infection by: 1) impeding the immune system; 2) preventing or accelerating bacterial growth; 3) altering antibiotic resistance and metal resistance mechanisms and 4) providing an ideal milieu for pathogens to proliferate in the necrotic tissues around the joint.

While distinguishing aseptic failure from PJI in a patient with an ALTR can represent a diagnostic challenge, diagnostic cutoffs have been suggested with higher synovial fluid white blood cell cutoffs than chronic PJIs without an ALTR; further, metallic debris can lead to errors in reading the synovial fluid cell count and differential and thus it is recommended to perform a manual cell count in cases of ALTR or metallosis [4]. Despite the vast body of literature investigating both ALTR and PJI following total joint arthroplasty independently, there is a lack of clinical data evaluating the concomitance of these phenomena.

A number of in vitro studies have assessed the effects of metal ion wear production on local soft tissue environment and immune response. Daou et al. noted that increased cobalt concentration in periprosthetic tissue resulted in an inhibitory effect on lymphocyte superoxide production, an impaired leukocyte recovery from acid stress and an improved intra-cellular survival of *Staphylococcus epidermidis* [5]. Akbar et al., likewise noted that high concentrations of cobalt and chromium ions produced an adverse effect on T-lymphocyte function, proliferation and survival [6]. In contrast, Hosman et al. found that high concentrations of cobalt and chromium have bacteriostatic effects as a result of inhibition of biofilm formation and bacterial proliferation [7].

Numerous case reports and small case series have highlighted the issue of concomitant ALTR and PJI [1,8–14]. In one dramatic example, Judd et. al. identified an infection rate of 33% in a series of nine patients revised for ALTR [8]. Two case reports describe concomitant ALTR and infection leading to massive necrosis of bone and soft tissue in a total of four patients, suggesting a possible link between ALTR and severe tissue damage from PJI [9,13].

Registry data from the Mayo Clinic reveals an increased risk of PJI among patients who underwent a primary MoM total total hip arthroplasty (MoM THA). Prieto et al. reported a 5.6% rate of revision for PJI in 124 patients who had undergone MoM THA [15]. While this exceeded the historical incidence of 1.3% and the authors postulate that the increased infection risk may be due to molecular effects of ALTR, they note that a causal relationship cannot be established since histologic evidence was not seen in all cases. Another study from the Mayo Clinic registry similarly noted an increased incidence of PJI requiring re-revision among patients revised for failed hip resurfacing. While not all of these revisions were directly attributed to ALTR, Wyles et al. did note that among eight patients revised for ALTR, two were found to be infected [16].

Multiple studies have identified a high incidence of PJI among patients being revised for ALTR [1,15–18]. However, few of these studies have provided a clear definition of how ALTR was diagnosed, and fewer still have utilized MusculoSkeletal Infection Society (MSIS) criteria to establish the diagnosis of PJI. Donell et al. reported a high rate of early failures in 652 MoM THAs with 90 (13.8%) hips revised over 9 years [1]. In their revision cohort, 9 patients (10%) were noted to have a deep infection. While intraoperative findings consistent with ALTR were described as 'sometimes seen,' no clear link was established between these findings and the cases of PJI.

Efforts to clearly define the features of septic MoM THA failures have contributed greatly to our understanding of the incidence of PJI in patients with ALTR. In a series of 104 MoM THA revisions, Grammatopolous et al. identified seven cases of PJI (6.7%) [19]. All PJI cases were strictly defined by the presence of positive cultures in two separate tissue samples and were noted to also have an ALTR. The use of more stringent criteria than MSIS guidelines led the authors to acknowledge that some cases of PJI could have been missed. The author concluded that the 6.7% incidence noted in their study was very high for presumed aseptic revisions as compared to a rate of 2.7% at their institution for a prior revision series with hard on soft bearings. In contrast, Kwon et al. reported on a cohort of 62 patients revised for ALTR, diagnosed based on clinical and MRI findings. Using MSIS criteria they identified seven cases of PJI (11%) which the authors felt were consistent with the published literature for revision of metal on polyethylene bearings citing prior studies.

There are a few studies that refute a possible link between ALTR and a higher incidence of PJI. Dimitriou et al., Liow et al. and Matharu et al. each reported PJI rates of 2% or less in their cohorts of 178, 102 and 64 ALTR revisions, respectively [20–22]. However, no description of the diagnostic criteria used to identify PJI was provided in any of these studies.

A growing body of both in vitro and clinical evidence suggests that ALTR may foster periprosthetic soft tissue changes that predispose to the development of PJIs. However due to small sample sizes, marked heterogeneity in study design and lack of consistent use of strictly defined diagnostic criteria, the quality of the evidence is currently limited. In conclusion, while conflicting evidence from few case series and some in vitro work make definitive conclusions difficult, the preponderance of the evidence suggests that the incidence of PJI is increased in this patient population.

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QUESTION 8: Should we routinely assess for serum/blood metal ion levels (cobalt (Co) and chromium (Cr)) when working up a patient with a painful total joint arthroplasty?

RECOMMENDATION: There is no data to suggest routine assessment of serum/blood metal ion levels (CoCr) in all patients with painful joint arthroplasty. There may be a rationale for second-line assessment of metal levels in painful metal-on-metal (MoM) total hip arthroplasty (THA), hip resurfacing, modular neck femoral components and in certain metal-on-polyethylene (MoP) THA in which trunnion corrosion is suspected.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

The reintroduction of MoM hip resurfacing and large head MoM THA had unforeseen complications related to elevated local Co and Cr levels. These levels could be associated with tissue necrosis, osteolysis, late dislocation, and rarely, systemic complications [1-3]. The assessment of metal levels in painful MoM THA, recalled MoM hip resurfacings and symptomatic modular neck THA is well accepted, and usually accompanied by advanced imaging techniques [1-4]. Metal ion levels are consistently higher than baseline following MoM THA or resurfacing, but there is no consensus on a "threshold" metal level for surgical intervention [5]. In fact, Matharu et al. reported better success at diagnosing adverse reactions to MoM THA/resurfacing if implant-specific thresholds are utilized [6]. Patients with MoP or metal-on-ceramic (MoC) hip arthroplasties have significantly lower blood ion concentrations than those with MoM bearings [5]. Rarely, deep infection of a MoM THA could occur concomitantly with tissue necrosis, metallosis and elevated serum metal levels. Typically, metal levels are obtained as a baseline in these cases after initial screening studies are obtained, such as serial radiographs and infection labs (i.e., erthyrocyte sedimentation rate (ESR) and C-reactive protein (CRP)). Certain aspects that may increase the suspicion for elevated metal levels include: CoCr head on a CoCr stem, high offset implants, vertically-oriented MoM cups, bilateral MoM-THA, female gender, increased activity, obesity, dual-modular implants (i.e., head-neck and neck-body junctions) and implants with a poor track record [7,8]. However, a recent case report did find an adverse local tissue reaction (ALTR) in a MoM THA without elevated serum metal levels [9].

Over the past five years, there have been several reports regarding corrosion of the modular metal femoral head-femoral stem trunnion junction [4,10-12]. The clinical picture of ALTR involves some type of hip symptoms (i.e., irritable hip, weakness, swelling, etc.), late dislocation or rarely systemic symptoms. It has been suggested that routine metal levels (i.e., Co and Cr) should be obtained in patients with symptomatic MoP THA. In several small series of patients, the diagnosis of ALTR associated with trunnion corrosion is associated with serum Co levels of >1ppb, with Co levels elevated above chromium levels [11,13]. The ESR and CRP may be elevated in up to 50% of patients with symptomatic trunnion corrosion, causing confusion with the possible diagnosis of infection [10,11]. There is some data that the MoP THA of certain manufacturers may be more likely to develop symptomatic trunnion corrosion [10,11,14,15]. In general, metal level assessments are typically a second or third line element of the painful MoP THA and, at present, due to the cost of these tests and the relatively low incidence of "trunnionosis," routine evaluation of these levels may not be indicated.

There is no data to recommend the routine assessment of metal levels in symptomatic patients with ceramic-on-ceramic THA, ceramic or oxidized zirconium-on-polyethylene THA, any total knee arthroplasty (TKA) or in other orthopaedic implants. Utilization as part of an algorithmic approach to the painful joint is acceptable; however, this should occur after more common causes of THA failure are explored first.

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QUESTION 9: How is a periprosthetic joint infection (PJI) diagnosed in the presence of adverse local tissue reaction (ALTR)?

RECOMMENDATION: The diagnosis of PJI in the presence of an ALTR is challenging as many of the commonly used tests for diagnosis (including the appearance of the surgical site) can be falsely positive. An aggressive approach to preoperative evaluation including an aspiration of the hip joint (sending the fluid for a manual synovial fluid white blood cell (WBC) count, differential and culture) is recommended. Testing the synovial fluid for leukocyte esterase (LE) appears as a feasible, inexpensive and reliable test for the diagnosis of PJIs in ALTRs. There is no supporting evidence for other synovial fluid biomarkers in the diagnosis of PJIs in the presence of ATLRs.

LEVEL OF EVIDENCE

Test	Strength
Clinical and radiological findings	Consensus. There is no supporting evidence for PJI diagnosis in ALTR
Serum markers (ESR and CRP)	Strong
Synovial fluid WBC count, manual and PMNs	Strong
Leukocyte esterase in synovial fluid	Moderate
CRP in synovial fluid	Limited
Other fluid biomarkers (i.e., α-defensin, IL-6, and IL-8)	Consensus: There is no supporting evidence for PJI diagnosis in ALTR

DELEGATE VOTE: Agree: 84%, Disagree: 7%, Abstain: 9% (Super Majority, Strong Consensus)

RATIONALE

ALTRs have become increasingly prevalent secondary to failed metal-on-metal (MoM) bearings and corrosion at the head-neck junction associated with metal-on-polyethylene (MoP) bearings [1,2]. Many of the signs and symptoms of ALTRs mimic PJIs including pain, limited range of motion, swelling around the hip and the appearance of purulent fluid seen intraoperatively or at the time of aspiration [3–5]. Furthermore, many of the commonly used markers for the diagnosis of PJI–including the erythryocyte sedimentation rate (ESR), C-reactive protein (CRP), synovial fluid WBC count with polymorphonuclear leukocyte (PMN) differential and synovial fluid alpha-defensin, have all been reported to have higher than expected rates of false positives in the setting of an ALTR. Hence, the diagnosis of PJI is very challenging in this scenario.

Clinical and radiological findings:

There is no supporting evidence for the accuracy of clinical and radiological (i.e., X-ray, CT and MRI) findings for the diagnosis of PJI in presence of ALTR. Nevertheless, by consensus these must be considered essentials for the initial diagnosis suspicion.

The first report to describe the challenges of diagnosing PJI in the setting of a failed MoM bearing was by Mikhael [4]. They reported two patients with failed MoM total hip arthroplasties (THAs). These two patients presented with pain and elevated serum inflammatory markers both of which mimicked an infectious presentation. Similarly, Cooper et al. described several patients eho had comparable presentations–including purulent appearing synovial fluid intraoperatively [2]. This was one of the first reports of symptomatic ALTR secondary to corrosion at the head-neck junction in a MoP bearing. Subsequently, several reports have noted that the synovial fluid WBC count and differential may be falsely positive in this setting. The authors note the false positives may be secondary to cellular debris causing errors in automated synovial WBC counts and differentials [6–8]. Therefore, in the case of an ALTR, a manual synovial fluid WBC count and differential is recommended [4–6,9].

Yi et al. conducted the largest study specifically focusing on the diagnosis of PJIs in hip revision due to an ALTR [7]. In this retrospective study, 150 consecutive failed THAs were reviewed. This study specifically noted the preoperative serum ESR and CRP and the synovial fluid WBC count and differential. A total of 19 of the patients met MusculoSkeletal Infection Society (MSIS) criteria for PJI. Of the 141 attempted synovial WBC counts, 47 of the samples (33%) had a synovial fluid WBC count that was deemed to be inaccurate or unreliable due to the presence of gross cellular debris, metallic debris, clots or some other abnormality in the specimen. They were able to conclude that automated synovial fluid WBC count was prone to false-positive results and should only be relied on if a manual cell count was performed [7]. In a similar study, Wyles et al. reported on 39 patients, of which four were deemed infected [10]. However, synovial fluid WBC count could not be performed in 33% of their samples due to specimen quality [10]. This led Wyles et al. to suggest that the differential was the best diagnostic test [6,10].

Synovial CRP has been suggested as a simple, cost-effective test for improving the diagnosis of PJI due to several reports finding elevated levels in the synovial fluid [11]. However, the cutoff value of synovial fluid CRP varied in each study: 2.8 mg/L, 3.65 mg/L, 6.6 mg/L, 9.5 mg/L, and 12.2 mg/L [12–14] and further research is needed to determine the utility of this measurement.

Tischler et al. reported on the use of a LE reagent test strip as an adjunct for the rapid diagnosis of PJIs. This study examined 76 patients being revised for a failed MoM bearing or corrosion at a modular junction [15]. Five patients were found to have a deep infection. Unfortunately, 15 of the samples had to be excluded as heavy discoloration of the synovial fluid made interpretation of the reagent strip unreliable, which is a known weakness of this testing modality [15,16]. While the LE strip had reasonable sensitivity (80%) and specificity (93%), the positive predictive value was poor at only

50% [15]. The negative predictive value was found to be 98%, however suggesting the utility of LE as a "rule out" test. Additionally, the LE strip test had the second strongest performance compared to sensitivity of synovial WBC count. Based on these results as well as results from other studies, LE test strips can be a valuable intraoperative test for differentiating PJI from aseptic failures [15,17,18].

Alpha-defensin has been proposed as an accurate test for the diagnosis of PJI due to its high sensitivity and specificity [19–24]. Okroj et al. conducted a multicenter retrospective review of 26 patients who had a diagnosis of ALTR, who had alpha-defensin testing performed [25]. One patient in the study met MSIS criteria for PJI. However, alpha-defensin was positive in 9 of 26 hips, including 8 that were falsely positive (31%). In addition to a positive alpha-defensin, all eight patients were positive on Synovasure. However, five of the eight positive Synovasure results included a warning that they may be falsely positive. Unfortunately, like the synovial fluid WBC count, alpha-defensin is prone to false positive results in the setting of ALTR [25].

Histopathology is often used for the diagnosis of PJI as recommended by the American Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guideline and as part of the MSIS criteria [26]. Grammatopoulos et al. studied 104 failed MoM THAs. They identified seven of the hips to be infected and suggested a standard criteria for the histopathologic diagnosis of PJI of greater than five PMN per high-powered field (PMN/HPF) [27].

Many studies on PJI diagnosis have recently shifted focus to synovial fluid, for it is the site of primary infection. Furthermore, use of synovial fluid to aid in the diagnosis is theoretically more sensitive than serum measurements. Many antimicrobial peptides and inflammatory cytokines have been proposed as synovial biomarkers indicating infection [21]. Among these are CRP, interleukin-1 (IL-1), IL-6, IL-8, IL-17A, interferon-γ, tumor necrosis factor and cathelicidin LL-37. The synovial fluid biomarkers alpha-defensin, IL-6 and IL-8 all demonstrated high sensitivity for diagnosing PJIs and potentially could be applied in combination for the diagnosis of PJIs [13,14,24]. However, studies are sparse and there is no supporting evidence of these biomarkers as tools for the diagnosis of PJI in cases of ALTR.

Given these findings, a more aggressive approach should be used when evaluating patients for PJI in the setting of an ALTR. Specifically, prior to revision surgery, aspiration of the hip joint is recommended to obtain cultures. These results may be incorporated into the evaluation in combination with a manual synovial fluid WBC count and differential. LE reagent strips can also be used as an adjunct to diagnosis, assuming the sample is not contaminated with excessive metal debris or blood rendering the strip unreliable. This approach gives the surgeon a preview of the appearance of the joint at the time of revision.

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2.3. DIAGNOSIS: LABORATORY TESTS

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QUESTION 1: What is an acceptable sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) for a diagnostic tool for periprosthetic joint infections (PJIs)?

RECOMMENDATION: The validity of a diagnostic tool is traditionally measured by sensitivity, specificity, PPV and NPV. A perfect diagnostic tool would be able to correctly classify 100% of patients with PJIs as infected and 100% of aseptic patients as non-infected. Without a perfect test available, we are left to balance between sensitivity and specificity; increasing one would reduce the other. To reduce the rates of false positives and negatives it is extremely important to take into account the pretest probability for infection, derived from patient risk factors, clinical examination and any other examinations available at the point of assessment.

Table 1. Variety of diagnostic tools for PJI

Variable	Sensitivity (95% CI)	Specificity (95% CI)	Positive Predictive Value (95% CI)	Negative Predictive Value (95% CI)
Serum testing	98.5%* (96.2-99.6)	100% (97.6-100)	100% (100-100)	97.5% (93.7-99.1)
Synovial fluid testing	100%* (98.3-100)	100% (85.2-100)	100% (100-100)	100% (100-100)
Intraoperative Findings	92.9% (80.5-98.5)	95.8% (78.8-99.9)	97.5% (85.1- 99.6)	88.5% (72.0-95.8)
Overall	96.9% (93.8-98.8)	99.5% (97.2-100)	100% (99.7-100)	96.7% (93.3-98.4)

CI, confidence interval
*Sensitivity for being diagnosed as infected or for moving forward for additional workup.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 79%, Disagree: 10%, Abstain: 11% (Super Majority, Strong Consensus)

RATIONALE

The validity of a diagnostic tool is traditionally measured by sensitivity, sensitivity, PPV and NPV. Validity is the accuracy of a test, or, whether a test measures what it is supposed to measure. A perfect diagnostic tool would be able to correctly classify 100% of patients with PJIs as infected and 100% of aseptic patients as non-infected. Without a perfect test available, we are left to balance between sensitivity and specificity; increasing one would reduce the other. To reduce the rates of false positives and negatives, it is extremely important to take into account the pretest probability for infection [1–3], derived from patient's risk factors, clinical exams and any other exams available at the point of assessment.

When approaching a patient with a failed total joint arthroplasty (TJA), PJI should always be kept in mind. At different points and timing of the investigation, we are willing to accept different sensitivities and specificities. In a recent study, a stepwise approach was used to develop an evidence-based algorithm for diagnosing PJIs. This stepwise approach enables us to maximize sensitivity and specificity for each step based on the timing of the encounter, previous tests available and invasiveness (Table 1).

In the first patient encounter, we typically rely on risk factors, clinical findings and simple serum markers to further guide us. At an early stage we want the tests to be a sensitive as possible, as misdiagnosing an infection as aseptic could lead to devastating outcomes. Interestingly, even if serum testing (as a screening tool) is negative, the risk for PJI is 2.5%. This emphasizes the importance of a pretest probability, patients with a high clinical suspicion based on timing from last surgery (< 2 years), number of surgeries on the joint and positive clinical findings such as erythema, tachycardia and reduced range of motion should be further investigated to increase sensitivity in this stage [4–7].

Synovial fluid aspiration is the next step in the investigation. In recent years numerous markers have been shown to be highly sensitive and specific [8–15]. The fact that patients undergoing synovial fluid testing are already identified as having a high risk for PJIs, the addition of the advantages of more knowledge about synovial fluid analysis garnered in recent years, allows the practitioner to have a very good performance test with high sensitivity (100%) and high specificity (100%). A majority of patients will be diagnosed in this stage.

When a definite diagnosis is not made by this point, intraoperative findings should be used to aid in the diagnosis. Patients not diagnosed as infected or aseptic at this point are usually patients with a dry tap or an overt infection in which the diagnosis is difficult. Thus, this stage holds a relatively low sensitivity and specificity and in 15% of the patients reaching this stage, a diagnosis cannot be made. These patients are often encountered in clinical practice and represent a real diagnostic challenge. Pointing out this unique group of patients promotes awareness in both clinical practice and calls for further research and novel technologies to reduce the number of patients in the gray area in an attempt to improve sensitivity and specificity in these borderline patients.

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QUESTION 2: Does the presence of both an erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) below the periprosthetic joint infection (PJI) thresholds rule out the diagnosis of a PJI?

RECOMMENDATION: Serum ESR and CRP levels below the threshold (as determined by the MusculoSkeletal Infection Society (MSIS) and International Consensus Meeting (ICM)) does not exclude the diagnosis of a PJI. Serum levels of ESR and CRP can be normal in some cases of PJI caused by slow-growing organisms.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 100%, Disagree: 0%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The diagnosis of PJI is one of the biggest challenges facing the orthopaedic community. There is no absolute test for diagnosis; hence, for a patient who is suspected to have a PJI, clinicians have to use a combination of tests. The first definition for PJI was developed by the MSIS that was later modified by the ICM on PJI in 2013. Based on this definition, the cutoff for ESR was defined as >30 mm/hr and >10mg/L and for CRP (>100 mg/L for acute PJIs) [1]. According to the diagnostic guidelines of the American Academy of Orthopaedic Surgeons (AAOS), serum ESR and CRP are the first line for screening patients who are suspected for PJI [2]. The document introducing the MSIS criteria for PJI explicitly stated that some of the diagnostic markers including ESR and CRP may be normal in the presence of PJI caused by slow-growing organisms that do not elicit physiological inflammation such as *Cutibacterium acnes (C. Acnes)* [3–5].

McArthur et al. [6] reported a 4% incidence of PJI cases that were seronegative (negative ESR and CRP). Most of the patients in this study who had PJI were infected with slow growing organisms including coagulase negative Staphylococcus, *C. acnes* and Corynebacterium. Three patients in their cohort were infected with virulent organisms; however, all had received antibiotics prior to their diagnostic workup. Nozdo et al. [7] reported that PJI cases with *C. acnes* induced a milder systemic response compared to methicillin-sensitive *Staphyloccous aureus* (MSSA) and that high clinical suspicion and prolonged cultures were essential to diagnose PJI in these patients. In another study by Figa et al. [8], authors showed that *C. acnes* PJIs had below threshold values for ESR and CRP in over half their cohort.

Combined ESR and CRP are also often falsely negative. Johnson et al. [9] reported an 11.1% false negative rate for combined ESR and CRP when the MSIS criteria were considered for diagnosis. Authors concluded that this is due to an insufficient inflammatory response mounted by certain patients with PJI, leading to the muted serological levels. Other studies were in line with this finding: Saleh et al. [10] concluded that combined ESR and CRP increased the specificity at a cost of sensitivity. Shahi et al. [11] reported the sensitivity and specificity of combined ESR and CRP to be 84 and 47%, respectively.

Administration of therapeutic antibiotics prior to diagnostic workups in PJI patients can also be a cause for falsely negative ESR and CRP. This can be an additional source of missed diagnosis of PJIs if only ESR and CRP are utilized for screening, as was shown in a study by Shahi et al. [12].

Diagnosis of acute PJI in the early postoperative period is also a challenge as these markers are usually elevated in this phase. Alijanipour et al. [13] did a retrospective study and investigated the suggested thresholds for serological markers. Authors concluded that a different threshold should be used for evaluating patients in the early postoperative period. In another study by Yi et al. [14],

authors reported that the optimal cutoff for diagnosing PJI in the early postoperative period should be higher than those that are traditionally used and recommended by the MSIS.

In conclusion, although serum ESR and CRP are the first line for screening PJI, a negative test result does not exclude the possibility of infection. Surgeons need to be cognizant of this fact and considering the huge burden of misdiagnosed PJIs, in presence of high clinical suspicion we recommend a comprehensive work up using combination of tests to refute or confirm the possibility of infection.

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QUESTION 3: What is the diagnostic accuracy and threshold of D-dimer in the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Recent literature supports the use of D-dimer as a serological marker for the diagnosis of PJIs. D-dimer has been shown to best perform at a threshold of 850 ng/mL. However, this threshold was determined internally from a cohort in a single institution study. Further studies are needed in order to validate this threshold or establish a more rigorous threshold.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 74%, Disagree: 16%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

Serological markers are typically the first line investigations in patients suspected of having PJIs [1]. Current practice as dictated by the American Academy of Orthopaedic Surgeons (AAOS) Clinical Practice Guidelines recommends the collection of blood for the measurement of serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). These tests fall short on multiple accounts. These tests may be falsely elevated in patients with a systemic inflammatory state or some other extra-articular infection [2,3]. Secondly, ESR and CRP may produce a false negative result in patients infected with low virulence organisms such as *Cutibacterium acnes* (*C. acnes*) [4]. Lastly, ESR and CRP may be physiologically elevated in the early postoperative period following the index arthroplasty procedure, making it difficult to interpret in the acute setting [5–7]. In light of these shortcomings, there is a clear need for alternative serological markers.

D-dimer, a fibrin degradation product, is a ubiquitous test that has been used as a screening test in patients with a suspected pulmonary embolism [8–10]. In a study by Shahi et al. [11], a consecutive series of 143 revision arthroplasties undergoing surgery for both septic and aseptic failure had blood drawn preoperatively and sent to the lab for serum measurements of D-dimer, ESR and CRP. Using the MusculoSkeletal Infection Society (MSIS) definition of PJI [12] as a gold standard and a D-dimer threshold of 850 ng/mL, D-dimer demonstrated a sensitivity and specificity of 89% and 93%. ESR and CRP demonstrated sensitivities of 73% and 79%, and specificities of 78% and 80%, respectively. In another study by Lee et al, serial blood draws were performed at baseline, postoperative days one, two, three and weeks two and six. Blood was sent for measurements of serum D-dimer, ESR and CRP [13]. Overall, ESR did not normalize until 6 weeks postoperatively while CRP remained elevated until 2 weeks after surgery. Serum D-dimer levels normalized by postoperative day 2. Thus the advantages of D-dimer are twofold: superior sensitivity and specificity, as well as a rapid decline to baseline levels following surgery, allowing for use in evaluation of a suspected acute PJI.

While it is clear that D-dimer outperformed both ESR and CRP at a threshold of 850 ng/mL, it is important to note that this threshold was calculated internally in order to maximize the

performance of D-dimer in this specific cohort. Larger cohorts are needed to not only further validate D-dimer as a serological marker of PJI, but also to develop a D-dimer threshold that can be used universally. Given its superior diagnostic performance and universal availability in hospitals, we recommend the routine use of D-dimer as part of the battery of serological markers used in evaluating a patient with suspected PJI.

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QUESTION 4: How does the level of leukocyte count and neutrophil percentage in the synovial fluid change with time following total joint arthroplasty?

RECOMMENDATION: The levels of leukocyte count and neutrophil percentage in the synovial fluid drop as one moves further away from the index arthroplasty. The latter is the rationale behind using different thresholds for these parameters in the diagnosis of acute versus chronic periprosthetic joint infections (PJIs).

LEVEL OF EVIDENCE: Limited

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

RATIONALE

We have recognized that the synovial composition changes as postoperative time increases, which is the reason for separate optimal cut-off values in the diagnosis of acute and chronic PJIs. During the last consensus meeting, the recommended cut-off value for the diagnosis of acute PJI (< 6 weeks from surgery) for synovial white blood cell (WBC) count was > 10,000 cells/μL and > 90% polymorphonuclear cells (PMNs) [1]. Likewise, the synovial fluid cut-off values for a chronic PJI were a WBC count > 3,000 cells/μL and > 80% PMNs [1]. When the optimal cut-off values are adjusted for the span of time after a procedure to differentiate an acute and chronic PJIs, synovial analysis remains a highly reliable diagnostic tool with similar diagnostic accuracy between acute and chronic PJIs.

Although adjustments in the WBC count and percentage of PMNs have improved the diagnostic accuracy for acute and chronic PJI, we have a limited understanding of the change in reliability of synovial analysis on a week-by-week basis. For instance, we do not have a strong understanding whether application of the same threshold two-weeks and six-weeks postoperatively has the same diagnostic reliability. Because we do not have literature to compare the proposed situation specifically, we must qualitatively compare two studies utilizing similar threshold cut-off values at different times postoperatively.

Kim et al. and Bedair et al. each investigated the diagnostic accuracy with similar optimal cut-off values from synovial analysis in the early postoperative period following primary total knee arthroplasty (TKA); however, each utilized differing patient inclusion criteria of three- and six-weeks, respectively [4, 6]. Applying a WBC count threshold of >11,200 cells/μL, Kim et al. had a sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of 100, 98.9, 65.4, and 100%, respectively [6]. Similarly, a percentage PMN threshold of >88% had a sensitivity, specificity, PPV, and NPV of 100, 65.6, 5.7, and 100%, respectively [6].

When compared to the diagnostic characteristics published by Bedair et al. (Table 1), the two studies demonstrate similar diagnostic accuracy for synovial WBC count and percentage PMNs. Therefore, increasing postoperative timespans appears to have limited influence on the diagnostic accuracy between three- and six-weeks from surgery. However, the same might not hold true for the diagnosis of chronic PJI.

Christensen et al. investigated the effect of increasing time intervals on synovial analysis in TKA patients who underwent aspiration as part of an evaluation for PJI and ultimately were determined not to have a PJI [7]. The authors investigated synovial analysis at ≤45 days, 45 to 90 days, 3 months to 1 year, and 1 to 2 years after surgery. Their data demonstrated synovial WBC count and percentage PMNs normalized between three months and one year after surgery [7]. As a result, it is possible increasing postoperative time intervals could alter the interpretation of synovial analysis in the setting of diagnosing a chronic PJI.

TABLE 1. Synovial cut-off values and associated test characteristics

Variable/Statistical Test	Acute Hip PJI [2]	Chronic Hip PJI [3]	Acute Knee PJI [4]	Chronic Knee PJI [5]
Cut-off Values WBC count (cells/μL); %PMNs	>12,800; >89%	>3,966; >80%	>10,700; >89%	>3000; >80%
Sensitivity (WBC count; %PMNs)	89%; 81%	89.5%; 92.1%	95%; 84%	80.6%; 83.9%
Specificity (WBC count; %PMNs)	100%; 90%	91.2%; 85.8%	91%; 69%	91.2%; 94.9%
Positive Predictive Value (WBC count; %PMNs)	100%; 91%	76.4%; 59.3%	62%; 29%	67.5%; 78.8%
Negative Predictive Value (WBC count; %PMNs)	88%; 79%	97.5%; 98.0%	99%; 97%	95.4%; 96.3%

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QUESTION 5: What is the role of alpha-defensin in the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Measurement of alpha-defensin in synovial fluid is a complement to existing diagnostic tests for PJIs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 82%, Disagree: 14%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Alpha-defensins are antimicrobial peptides released by neutrophils in response to pathogens. They can be measured in synovial fluid and have been proposed as an indicator for PJI. Alpha-defensin use as a PJI diagnostic marker was introduced first by Deirmengian et al. in 2014 [1].

There are two commercially available methods for measuring alpha-defensin in synovial fluid: (1) the enzyme-linked immunosorbent assay-based alpha-defensin immunoassay (Zimmer Biomet, Warsaw, IN, USA), which gives a numeric readout within 24 hours and (2) the alpha-defensin lateral flow test (Zimmer Biomet, Warsaw, IN, USA), which gives a binary readout within minutes. Both assays were developed with the intention of matching the MusculoSkeletal Infection Society (MSIS) criteria as the gold standard for diagnosis of PJI.

The Alpha-defensin Laboratory Test

The alpha-defensin laboratory-based immunoassay measures the alpha-defensin concentration in synovial fluid, providing results relative to a signal/cutoff ratio of one. This form of the assay has been studied at numerous institutions, including The Rothman Institute [1], The Mayo Clinic in Arizona [2], The Cleveland Clinic (Cleveland) [3], the Cleveland Clinic (Florida) [4] and the HELIOS ENDO-Klinik [5]. The following table demonstrates the results of these studies. Both the sensitivity and specificity of the alpha-defensin laboratory test exceed 95% when using the MSIS consensus criteria for PJI as a gold standard.

In addition to individual studies, there have been meta-analyses of the alpha-defensin laboratory test. Lee et al. [6] performed a meta-analysis of the performance of the synovial fluid leukocyte count, polymorphonuclear (PMN) %, C-reactive protein (CRP), alpha-defensin, leukocyte esterase, Interleukin-6 (IL-6), IL-8 and culture in diagnosing PJI. They found the alpha-defensin laboratory test to demonstrate the highest sensitivity (97%) of any individual test for PJI. No other test in this meta-analysis had a sensitivity >90%. In this same study, the alpha-defensin test was found to demonstrate the highest specificity (96%) of any individual test for PJI. A meta-

TABLE 1. Institutions studying the alpha-defensin laboratory-based immunoassay

Institution	N	Gold Standard	Sensitivity	Specificity
Rothman Institute	149	MSIS Criteria	97% (3637)	96% (107/112)
Mayo Clinic Arizona	61	MSIS Criteria	100% (33/33)	95% (83/87)
Cleveland Clinic	111	MSIS Criteria	100% (24/24)	98% (53/54)
HELIOS ENDO-Klinik	156	MSIS Criteria	97% (28/29)	97% (123/127)
Cleveland Clinic Florida	70	MSIS Criteria	97% (34/35)	97% (34/35)
Combined	**547**		**98.1% (95%CI: 95-100%)**	**96.4% (95%CI:94-98%)**

analysis by Yuan et al. [7] found that the alpha-defensin test had a sensitivity of 96% and a specificity of 95%. Similarly, a meta-analysis by Li et al. [8] demonstrated a sensitivity of 98% and a specificity of 97%.

The Alpha-defensin Lateral Flow Test

The alpha-defensin lateral-flow test is a rapid test that can be performed in the operating room. The user must follow the device directions and apply synovial fluid, followed by a waiting period which demonstrated the presence or absence of a line. The presence of a line is indicative of a positive test. Obviously, the results of this device not only depend on the inherent diagnostic characteristics of the test, but also compliance with the directions of use. The literature reporting on the performance of the alpha-defensin lateral flow test is not as consistent or controlled as the literature on the laboratory test. For example, whereas all the major studies reporting on the laboratory test are relatively large and utilize the MSIS criteria as a gold standard, the studies reporting on the lateral flow assay are greatly varied in the number of patients and do not all strictly utilize the MSIS or International Consensus Meeting (ICM) criteria.

Four small studies, each with very few PJIs and very large confidence intervals (CIs), reported on their initial experience with the alpha-defensin lateral flow test. Below is a table summarizing their results. It is important to note that the report by Sigmund et al. [9] was methodologically limited by an absence of availability of the synovial fluid white blood cell (WBC) and PMN % for diagnosis, and also by the inclusion of a very large number of spacer block aspirates. Both Kasparek et al. [10] and Sigmund et al. [9] suggested that the alpha-defensin lateral flow test could be used in place of frozen section histology intraoperatively, given the apparent equivalence between the methods in their studies. However, given the very small numbers and very large confidence intervals in these four studies, it is difficult to draw any significant conclusions.

TABLE 2. Smaller studies reporting on the alpha-defensin laterial flow test

Author	N	PJIs	Gold Standard	Sensitivity (95%CI)	Specificity (95%CI)
Kasparek et al.[10]	40	12	ICM	67% (35-89)	93% (75-99)
Sigmund et al.[9]	50	13	Modified MSIS	69% (46-92)	94% (84-100)
Suda et al.[11]	30	13	MSIS	77% (no range)	82% (no range)
Balato et al.[12]	51	16	ICM	88% (75-95)	97% (87-100)

There are also three large studies of the alpha-defensin lateral flow test that utilize the MSIS criteria as a gold standard. Below are the summarized results of their results in a table format. The report by Renz et al. [13] did include alternative results when compared to other diagnostic criteria, but for the purposes of remaining consistent, only MSIS criteria-based results are included in this Table 3.

TABLE 3. Larger studies reporting on the alpha-defensin laterial flow test

Author	N	PJIs	Gold Standard	Sensitivity (95%CI)	Specificity (95%CI)
Berger et al.[14]	121	34	MSIS	97% (85-100)	97% (90-99)
Gehrke et al.[15]	223	76	MSIS	92% (84-97)	100% (97-100)
Renz et al.[13]	212	45	MSIS	84% (71-94) 94% excluding sinuses	96% (92-99)

There are two studies attempting to use meta-analysis techniques to evaluate the lateral-flow test. One, by Suen et al. [16], does not include the recent large studies by Gehrke et al. [15], Berger et al. [14] or Renz et al. [13]. Furthermore, they included the report by Sigmund et al. [9] which is problematic due to the lack of diagnostic data and inclusion of a very large population of spacer block aspirates. A second study by Eriksson et al. [17], is similarly limited in that recent large studies are not included but includes the potentially limited study by Sigmund et al. [9].

Special Considerations

The alpha-defensin immunoassay test seems not to be influenced by prior administration of antibiotics and covers a wide spectrum of potential pathogens causing PJI [18,19]. Additionally, its results do not appear to be affected by patient-related factors such

the presence of inflammatory diseases [White Paper Synovasure alpha-defensin; CD Diagnostics, Claymont, DE, USA].

Given that the alpha-defensin tests are protein immunoassays, it is critically important that the fluid tested is actually synovial fluid. Aspirates resulting from a saline lavage are not appropriate for any biomarker testing. Furthermore, while blood contamination does not appear to alter the results of the alpha-defensin test, it is critical that the aspirate is actually synovial fluid, and not pure blood from a postoperative hematoma. The following are general precautions when utilizing the alpha-defensin test.

1. Do not request the test when the aspirated sample is from a saline lavage.
2. Pure blood aspirates (e.g., postoperative hematomas) should not be sent for biomarker testing. However, simple blood contamination does not appear to affect the test.
3. Aspirates from prosthetic joints with metallosis demonstrate approximately a 30% false positive alpha-defensin rate.
4. False-negative alpha-defensin results may be observed in the setting of a sinus tract (similar to that observed for the leukocyte count). Fortunately, a joint arthroplasty with a sinus tract is accepted by all criteria for PJI to be deterministic of the diagnosis of PJI. Therefore, a false-negative alpha-defensin result in the setting of a sinus tract should not cause a false diagnosis or be detrimental to patient care.
5. Immediate postoperative aspirates rarely demonstrate mature synovial fluid but are more likely to consist of hematoma. Biomarker assays should not be utilized in the first four to six weeks after surgery.
6. The alpha-defensin test has not been validated for use in the setting of a spacer block.

Summary

Appropriate use of the alpha-defensin test should be exercised. It is not intended to be utilized from aspirates from a saline lavage, gross postoperative hematoma, spacer block or a joint with a sinus tract. Furthermore, the test should be used with proper expectations in the setting of metallosis, as false positive testing appears to be demonstrated at a rate of 30%.

The alpha-defensin laboratory test appears to be the most sensitive and specific single test for PJI and therefore appears suitable to be included in the armamentarium of tests routinely used. Given its combination of a high sensitivity and high specificity as demonstrated in multiple institutions and meta-analysis, it serves well as both a good rule-in and rule-out test and could be given significant weight compared to other individual tests.

The alpha-defensin lateral flow test demonstrates results which appear at least equivalent to frozen section histology, providing for a more rapid and convenient intraoperative solution. Although several smaller studies suggest that the lateral flow test is substantially less sensitive than the laboratory assay, larger studies suggest that the sensitivity is only marginally less sensitive, but remains above 90%. The big advantages of the lateral flow test are that it can be utilized perioperatively and that it gives results within minutes. These features make the lateral flow test useful in ruling-in infection. These results must be carefully interpreted when they show negative results. Although further studies are needed to define the exact sensitivity of the lateral flow test, it appears to be the most accurate rapid test for PJI.

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QUESTION 6: What is the diagnostic accuracy of histologic tests and thresholds used in the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: There is a variability of the histologic examination of intraoperative frozen sections as well as the thresholds used for the presence of neutrophils. The preparation and interpretation of frozen sections can be highly operator-dependent.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

A recently published meta-analysis of longitudinal studies that compared histologic results with simultaneously obtained microbiologic cultures by Tsaras et al. 2012 [2] included 26 studies, published between 1982 and 2009 and included 3,269 patients who had undergone hip or knee arthroplasty. Of those patients, 796 (24.3%) had a culture-positive PJI. Using the diagnostic criteria chosen by the investigating pathologist, the pooled data showed that a positive result from a frozen section by histopathology predicted a 75% (95% confidence interval (CI), 67-82) probability of a positive culture infection and a negative frozen section result predicted a 5% (95% CI, 4-8) probability of a culture-positive infection. In 15 studies, the threshold of 5 polymorphonuclear leukocytes (PMN) per high power fields (HPF) in each of at least 5 HPF to define a positive frozen section had a diagnostic odds ratio (OR) of 52.6 (95% CI, 23.7 – 116.2), while 6 studied the threshold of 10 PMNs per HPF and had a diagnostic OR of 69.8 (95% CI, 33.6-145). No statistically significant difference between the two thresholds was found. The authors concluded that intraoperative frozen section histologic evaluation was very good at predicting a diagnosis of culture-positive PJI and had a moderate accuracy in ruling out the diagnosis of PJI.

Corresponding results of a meta-analysis of the accuracy10 vs. 5 PMNs as a threshold in frozen sections to diagnose PJIs was published by Zhao et al. in 2013 [3]. The meta-analysis includes 12 studies, published between 1972 and 2012, involving 1,011 patients undergoing hip arthroplasty of which 194 (19.2%) patients had a PJI. In 7 studies, the threshold of 5 PMNs per HPF was used, in 2 studies, the threshold of 10 PMNs per high-power field was used, while in 3 studies, both thresholds were used. The diagnostic OR was 23.5 (95% CI, 10.5 – 52.7) when 5 PMNs per HPF was used and 35 (95% CI, 7.7– 159.3), when 10 PMNs per HPF was used. Equally, they found no statistically significant difference between the two thresholds. The authors concluded that their results indicates that though both thresholds are stable and effective, a threshold of 10 PMNs per HPF is better for diagnosing PJI.

Since the meta-analysis included studies until 2009 [2], 17 studies [4–20] have been published from 2010 to 2017 and considered as relevant to the question about the accuracy of the method. These studies show a variability of the accuracy between 65.6 and 99%, a sensitivity between 38.8 and 96.6% and a specificity between 77 and 100% [4–20]. The studies were performed at single centers, and the majority of the studies included less than 100 patients of which less than 25 patients were infected.

The accuracy value of thresholds in the meta-analysis by Zhao et al. in 2013 [3] was 85.2% (95% C,I 79.3-91.1) when 5 PMNs per HPF was used and 89.1 (95% CI, 80.5– 97.7), when 10 PMNs per HPF was used. The true positive rate (sensitivity) was 0.67 (95% CI, 0.49-0.86) and 0.6 (95% CI, 0.27-0.93) for 5 PMNs per HPF and 10 PMNs HPF, respectively. The corresponding figures for the true negative rate (specificity) was 0.9 (95% CI, 0.85-0.96) and 0.93 (95% CI, 0.85-1.0).

The results of the meta-analysis [2,3] of the thresholds show wide 95% CI in the diagnostic OR for the 5 and 10 PMNs per HPF, respectively. This may indicate small sample sizes that may not be able to show a difference that exists.

Nevertheless, adequate published evidence exists to support diagnostic thresholds of either 5 PMN in each of 5, 40X HPF (maximum tissue concentration) or 10 PMN in each of 5 HPF to help diagnose or rule-out periprosthetic infection at revision arthroplasty. Exceptions exist, but in general, increasing the concentration of PMN required for diagnosing infection from 5 to 10 PMN per HPF may slightly increase specificity but have little effect on sensitivity. A few studies have advocated using lower PMN concentrations to maximize sensitivity [13,19]. The studies reviewed apply only to tissue obtained at revision arthroplasty of the hip or knee; different optimum thresholds may exist for the shoulder or other sites.

Kashima and his co-workers [21] found that all cases of aseptic loosening contained fewer than 2 PMNs per HPF and that in some cases of septic loosening, fewer than, on average, 5 PMNs per HPF are present in periprosthetic tissues. The study included 76 patients of which 22 were infected. The histological criterion of more than 2 PMNs per HPF showed increased sensitivity and accuracy for the diagnosis of septic loosening. The sensitivity, specificity, and accuracy for +++ neutrophil polymorph infiltration was 83, 96 and 91 %, respectively, and for >++ neutrophil polymorphs 94, 96 and 97 %, respectively. In their conclusion, they suggest that the MusculoSkeletal Infection Society (MSIS) histological criterion of more than 5 PMNs per HPF is too high an index figure for the diagnosis of all cases of hip and knee arthroplasty infection.

Limitations

It is likely that the method of tissue sampling by the surgeon and the experience of the pathologist influence the value of frozen sections obtained at revision arthroplasty. For example, it has been suggested that PMNs entrapped in superficial fibrin or migrating from capillaries in granulation tissue should not be included in the PMN quantification. Pathologists should also avoid misinterpreting granulocyte precursors in the hematopoietic bone marrow that often accompanies these biopsies as suggestive of infection and it can be difficult to distinguish eosinophils from neutrophils in some frozen sections. The microscopic fields selected for PMN quantification should represent the maximum neutrophil concentration, not the overall average on the microscope slide, and tissue obtained from near a recent periprosthetic fracture may contain neutrophils unrelated to infection. Many of the reports in this review fail to specify the above limitations, so subtle differences in the routine practice of pathologists in different centers may contribute to the variable quality of frozen section (FS) interpretation [22]. In addition, the reference standard against which FS interpretation has been meas-

ured has not been consistent. Some authors have considered one positive culture as indicating infection, others have required additional factors or have used the MSIS criteria [7] Other studies have recognized that long-term clinical follow-up may be needed to define clinically relevant periprosthetic infections, especially those involving organisms of low-virulence [23].

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QUESTION 7: What is the role of specific granulocyte counting methods and new immunohistologic staining techniques in diagnosing periprosthetic joint infection (PJI)?

RECOMMENDATION: The role of specific granulocyte counting methods and new immunohistologic staining techniques is to support the diagnosis of infection when diagnosis is uncertain. The recommended threshold is 5 or more polymorphonuclear leukocytes (PMNs) per field in each of 5 high power (400x objective) magnification fields. The stains reported-to-date can only be performed on sections of formalin-fixed, paraffin embedded tissue. Therefore, they are not available for use on frozen sections obtained during an operation.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 85%, Disagree: 4%, Abstain: 11% (Super Majority, Strong Consensus)

RATIONALE

Currently, histology has been considered as one of the variables for PJI diagnosis [1]. Literature has reported on tissue reaction associated with implant failure and its relationship with infection [2]. It has been seen that an increase of PMNs correlates with the presence of an active infection [3,4]. New methods have been introduced to increase diagnostic performance. A literature search of PubMed, Ovid, Embase and the Cochrane Library was performed to include studies that evaluated the role of granulocyte counting methods and/or evaluating new immunohistologic staining techniques. The following types of studies were excluded:

1. Studies with histology metrics were used as the gold standard to test the results of other tests.
2. Studies involving primarily sites other than hip or knee (for example, shoulder operations are excluded).
3. Reviewed articles and case reports.
4. Articles published in languages other than English.

5. Articles with only limited data available such that one cannot calculate the sensitivity, specificity or predictive value of histology.
6. Studies which analyze different aspects of inflammation and therefore have no focus on the diagnostic quantification of granulocytes.

For each, it was attempted to define the results of histology and the influence of special or immunohistochemical stains with respect to true positives, false positives, true negatives and false negatives to calculate sensitivity, specificity, predictive value and accuracy. If that data was unavailable, the values reported by the authors were recorded. The threshold used for interpreting histology as favoring infection, the reference standard and other clinical metrics were also recorded.

Results

The initial search yielded 287 articles, 41 of which were automatically excluded as duplicates. The titles and abstracts of the remaining 246 articles were reviewed and 233 excluded. The remaining 13 articles, reviewed in their entirety, and 9 publications for excluded for the following reasons: 3 were not in English, 3 related to aseptic loosening (not infection), 1 did not involve the use of special stains and 2 had an inappropriate study design. The remaining three [5–7] studies were included in our review:

1. Kashima TG, Inagaki Y, Grammatopoulos G, Athanasou NA. Use of chloroacetate esterase staining for the histological diagnosis of prosthetic joint infection. Virchows Arch. 2015;466:595–601. doi:10.1007/s00428-015-1722-y.
2. Krenn VT, Liebisch M, Kölbel B, Renz N, Gehrke T, Huber M, et al. CD15 focus score: Infection diagnosis and stratification into low-virulence and high-virulence microbial pathogens in periprosthetic joint infection. Pathol Res Pract. 2017;213:541–547. doi:10.1016/j.prp.2017.01.002.
3. Munemoto M, Inagaki Y, Tanaka Y, Grammatopoulos G, Athanasou NA. Quantification of neutrophil polymorphs in infected and noninfected second-stage revision hip arthroplasties. Hip Int. 2016;26:327–330. doi:10.5301/hipint.5000365.

Based on the review of the literature, it is recommended that neutrophil counting methods be included when diagnosis is uncertain. In general, we recommend that 5 or more PMNs per field in each of 5 high power (400 X objective) magnification fields be used as the threshold to support the diagnosis of infection. Additional studies are needed to determine the optimum use of special stains. Although the literature supports the use of special stains for neutrophils to increase sensitivity, the stains reported to date can only be performed on sections of formalin-fixed, paraffin embedded tissue. Therefore, these stains are not available for use on frozen sections obtained during an operation. There is some evidence that findings derived from special stains can also correlate with the virulence of the pathogens involved in the infection.

The above recommendations are based on the review of three studies, one of which is high quality. Based on the range of sensitivity and specificity, the strength of the 5 PMNs threshold is strong, while the advocacy of special stains on permanent sections is moderate.

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2.4. DIAGNOSIS: PATHOGEN ISOLATION, CUTURE RELATED

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QUESTION 1: Should intraoperative cultures be taken during every revision total joint arthroplasty (RTJA)? If so, how many?

RECOMMENDATION: Yes, routine cultures should be taken during every RTJA. At least three intraoperative culture samples should be obtained.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 87%, Disagree: 12%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Using the following search terms and words (revision and joint infection; joint arthroplasty; aseptic loosening and culture), a total of 1,772 results were generated from PubMed, Ovid and Google Scholar. Sixty-five studies were found to have met the inclusion criteria. Publications that did not relate to the topic, case reports and those describing technical details of revision arthroplasty were all excluded. Furthermore, registry studies, articles with inadequate description of tissue sample methodology and studies with few patient numbers were

TABLE 1. Statistical analysis by minimum number of cultures sent per revision TJA (RTJA)

Minimum Number Cultures Sent (Mean)	Total Number of RTJA, n (# of Studies)	Sensitivity, % (Lower-Upper CI)	Specificity, % (Lower-Upper CI)	PPV, % (Lower-Upper CI)	NPV, % (Lower-Upper CI)
<3	2,038 (9)	72 (63-81)	94 (90-98)	80 (58-102)	79 (69-89)
≥3	2,283 (14)	62 (50-74)	93 (88-98)	78 (66-90)	85 (78-92)
Overall	4,321 (23)	66 (58-75)	94 (90-97)	78 (67-89)	83 (77-89)

also excluded. To ensure an acceptable strong to moderate strength body of literature evidence – only prospective, comparative and large retrospective studies were included. The literature search did not yield any randomized controlled trials. Across the studies which met the criteria, two that stated multiple tissue samples were taken and were recorded as at least two samples (due to lack of clarity on the number). In order to determine the optimal number of culture samples to be obtained intraoperatively, we included only studies with revision hip and knee arthroplasty that documented the total number of cultures taken at time of surgery and the corresponding diagnostic accuracy (sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV)). The studies were then stratified according to the number of samples sent. Exclusion criteria were studies that did not include all four values of sensitivity, specificity, PPV and NPV. The number of cultures obtained and sent were reported as the mean of the minimum number of cultures sent, as reported in the studies. A meta-analysis was performed to obtain pooled estimates for specificity, sensitivity, PPV and NPV using exact likelihood methods normal-binomial model with empirical ("sandwich") variance estimator. Separate estimates were obtained for studies reporting < 3 cultures and those reporting ≥ 3 cultures.

The reviewed literature revealed that the mean number of culture samples taken across cohorts included in the studies was four (minimum two, maximum eight). There were 23 studies with a total of 4,321 patients undergoing revision hip and knee arthroplasty that documented the total number of cultures taken at time of surgery and the corresponding diagnostic accuracy (sensitivity, specificity, PPV and NPV). The analysis indicated that taking three or more intraoperative samples yielded higher negative predictive value to rule out infection without limiting the positive predictive value to confirm infection (Table 1). It is a known fact that periprosthetic joint infection (PJI) may be present in patients undergoing revision hip and knee surgery for aseptic etiologies, even when preoperative workup suggests that this might be the case. A varying degree of clinically relevant PJI has been associated with presumed aseptic loosening [1,2]. These cases were diagnosed from intraoperative cultures. It is for this reason that we suggest that intraoperative samples be sent for all revision hip and knee arthroplasties, irrespective of preoperative diagnosis.

Up to 12% of cases of total knee and hip arthroplasty (TKA and THA) are revised within ten years. Cases are revised for a variety of reasons, and making a preoperative diagnosis may be challenging [1]. PJI is one of the most morbid complications after total hip and knee arthroplasty. According to the Swedish Hip Arthroplasty Register between 2000 and 2013 the risk of PJI increased from 7.5-13.5%. In patients undergoing revision for an aseptic diagnosis after TKA and THA, 7.9 and 12.1%, respectively, had PJIs [2]. As no gold standard exits for the diagnosis of PJI, clinicians often must rely on a combination of tests to confirm or rule out a diagnosis [3]. There is also a paucity of available standards on how many intraoperative cultures should be taken. Attempts to standardize these practices have been published in the form of treatment guidelines, yet the approach still varies between practitioners and locations. This is in part owing to a paucity of strong evidence to support specific guidelines [4].

Atkins et al. had recommended that five or six intraoperative specimens be sent and that the cutoff for a definite diagnosis of PJI be three or more operative specimens positive for an indistinguishable organism due to the low sensitivity of cultures [5]. Some studies reported on their results when taking five to six intraoperative tissue samples from multiple areas of the infected prosthesis and hip joint including the capsule, pericapsular tissue and membrane around prosthesis. However, some other studies were carried out using a protocol where two to three tissue samples were taken intraoperatively for microbiology culture analysis [2,6–8]. Our present review of the literature shows an average of four tissue samples being taken across the studies which we examined. This is consistent with 25% of the cohort of studies assessed in this review.

There are obvious discrepancies and variations in the protocols and guidelines being adhered to which may vary according to institution. If patients with PJI can be accurately identified preoperatively or intraoperatively, a better outcome might be achieved from revision surgery. Although a combination of preoperative investigations can point towards infection, no test has yet proved to be completely accurate as a stand-alone test [9]. Therefore due to low sensitivity of intraoperative cultures [10], it is only imperative that definite guidelines on how many samples to be taken should be anchored on evidence based literature. In the current body of published studies, there are no randomized controlled studies answering this specific question.

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QUESTION 2: Are there significant differences in the yield of culture between preoperative aspiration and intraoperative culture samples? If so, which result should be utilized?

RECOMMENDATION: There may be differences in the yield of culture between preoperative aspiration and intraoperative culture samples, particularly in the case of polymicrobial infections or low-virulence organisms. The collection of multiple intraoperative tissue samples is considered by many experts to provide the highest yield in isolating organisms from a joint.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

When interpreting culture results in general, one should be aware that the literature demonstrates a lack of reproducibility, whether from the synovial fluid or from the tissue.

Due to inherent methodologic difficulties and limitations in the existing literature and variation in culture techniques between institutions, it is not possible to make a general statement regarding the relative yields of synovial fluid and tissue culture. In general, we recommend that synovial fluid and tissue samples both be sent for culture, as the growth of an organism from either source is highly informative. However, clinicians should be aware that in general, culture techniques have a relatively poor sensitivity for periprosthetic joint infections (PJIs) (40 to 85%), and that negative culture results do not rule out PJI. The current literature does not provide evidence-based guidance on how to interpret contradictory synovial fluid versus tissue culture results. Considerable research is needed to optimize and standardize culture techniques to provide improved yield for isolation of infective organisms.

There are inherent methodologic difficulties in studying the comparative yield between synovial fluid and tissue culture results. First is the fact that while synovial fluid is usually sent to the lab for a single culture, intraoperative tissue samples are usually sent in multiples. Whenever a diagnostic test is completed multiple times and the results are interpreted in combination, the sensitivity increases and the specificity decreases by definition. Therefore, even if the sensitivity and specificity of synovial fluid and tissue culture were identical, the multiplicity of testing associated with tissue culture sampling would result in the observation that intraoperative culture has a higher yield. Tissue samples have a greater opportunity to yield a positive result, whether real or due to contamination.

Second, is the fact that there are no universal standards in arthroplasty culture technique. The collection, transport, sample preparation, culture media and culture times vary greatly between institutions [1-18]. The techniques may even vary based on whether the sample is a fluid or a tissue sample at the same institution. Therefore, the results published at one institution regarding the yield of synovial fluid culture or tissue culture cannot be assumed to apply to all institutions.

Third, is the fact that the definition of PJI has varied over time and had great variability before the MusculoSkeletal Infection Society (MSIS) definition. Many historical studies considered positive tissue cultures to be the gold standard for infection, eliminating the possibility of properly assessing the diagnostic characteristics of tissue culture. Furthermore, different centers have different definitions of what qualifies as a positive tissue culture, with variation in the number of positive samples requirements, the virulence of the organisms yielded and the assessment of broth-only results.

Microorganisms involved in infection of orthopaedic devices are highly adapted on the implant or in the bone-cement interphase, adhering to the environment within the in vivo biofilm, but are only to a minor part in a planktonic state in the synovial fluid [19]. This fact can explain the high rates of preoperative aspiration with false negative bacteriology [11]. Moreover, other factors such as bacterial load or the type of germ may affect synovial culture, which may explain the higher sensitivity of aspiration fluid culture observed in acute versus chronic infections [20, 21]. Although a recent study from Shanmugasundaram et al. could not show any influence of microbial virulence on organism isolation from preoperative aspiration versus intraoperative culture [14], some studies showed insufficient accuracy of synovial fluid culture in isolating low virulent pathogens in chronic PJI compared to intraoperative tissue culture [11, 21].

For the aforementioned reasons, a comparison of the yield of synovial fluid versus tissue cultures cannot be made with any confidence. There are exceedingly few studies comparing the culture sensitivity of synovial fluid versus tissue [1-18]. Of these reports in the literature, there are very significant limitations which prevent the appropriate comparison of synovial fluid versus tissue culture yield. Many of these studies have fewer than 10 patients with PJI. The diagnosis of PJI varies greatly in these studies. And many of these studies fail to provide the proper data in evaluating their analysis and conclusions. Studies seeking to compare synovial aspiration and intraoperative tissue culture results have shown a wide range of concordance (57-92%) [1-18] in the sense of false-negative, false-positive, true-negative and true-positive results. Among these 18 studies, nine were retrospective and nine collected their data prospectively.

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QUESTION 3: Do bone cultures provide additional diagnostic accuracy in the diagnosis of periprosthetic joint infections (PJIs)?

RECOMMENDATION: Inconclusive. We cannot recommend for or against bone biopsy to provide additional diagnostic accuracy in the diagnosis of PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 5%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Use of traditional culture remains the preferred method for isolation of the infecting organism(s) in PJIs. It is reasonable to assume that increasing the number of samples and taking culture from "representative areas of infection" enhances the yield of culture in isolating the infective organism. Current data supports obtaining synovial fluid and tissue samples for culture, with studies showing tissue to have a better yield than synovial fluid and is preferred over swabs [1,2]. Whether the tissue culture should include bone also has not been well studied. In general, multiple samples improve diagnostic accuracy [3]. Most data supports obtaining at least three distinct and as many as six intraoperative samples for culture [2,4]. The site of specimen retrieval includes the synovium, as well as tissue from the femur and tibia in the knee or the femur and the acetabulum in the hip. In addition to traditional cultures, sonication of implants has been shown to possibly increase chance of identifying the organism [5-7].

Only one study addresses the role of utilizing bone biopsy in the detection of infection in joint arthroplasty. In a prospective cohort study, Larsen et al. [8] assess the contribution of different specimen types in detecting PJI. It was found that bone biopsy did not provide any additional information and did not contribute independently to the diagnosis of infection. The bone biopsy was obtained from bone in contact with the prosthesis. Only 9 of 32 samples (28%) resulted in a positive culture after 6 days. This increased to 13 of 32 at 14 days. This was considerably less than soft tissue biopsies which resulted in 37 of 42 (88%) positive cultures. There were no cases where bone biopsy yielded a positive culture independent of soft tissue biopsy. This resulted in a negative likelihood ratio of 0.6 (95% confidence interval (CI), 0.5-0.8) which only slightly decreases the probability of infection with a negative result. This study found the optimal specimen set for diagnosis of periprosthetic joint infection included joint fluid, prosthetic component and five soft tissue biopsies [8].

Other studies have assessed the role of bone biopsy in detecting osteomyelitis and septic arthritis. Bone biopsy in osteomyelitis was found to have significantly improved sensitivity, specificity and predictive value in determining the etiological organism when compared to sinus tract biopsy [9] and soft-tissue and deep wound biopsy [10]. In the setting of septic arthritis, sampling of the ileum

and proximal femur resulted in significantly increased positive culture rates when compared to aspiration of synovial fluid alone [11]. However, it is difficult to extrapolate these findings to assume that obtaining a bone sample in a patient with PJI is likely to increase the yield of culture. In the absence of adequate data, we have refrained from recommending that bone samples for culture should be taken routinely in patients with PJIs.

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QUESTION 4: Is there a role for obtaining cultures before, and at the time of, insertion of prosthesis during second stage (reimplantation) of a two-stage exchange arthroplasty?

RECOMMENDATION: Preoperative aspiration of a joint should be determined based on the index of suspicion for persistent infection. During reimplantation, however, multiple fluid and tissue samples should be sent for culture. There is a direct correlation between the outcome of two-stage exchange arthroplasty and culture results during reimplantation.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Two-stage exchange arthroplasty consists of removal of the infected prosthesis in the first stage, usually replacing it by an antibiotic-loaded cement spacer and treatment with systemic antibiotics. Once the infection is thought to be under control, the second-stage of reimplantation is performed. The metrics that determine the optimal timing of reimplantation are not known. However, many surgeons rely on a combination of metrics that may include aspiration of the joint prior to reimplantation. The exact role of preoperative joint aspiration prior to reimplantation remains undefined. Furthermore, there is also no specific test to determine if the infection has or has not been controlled.

Although aspiration of a joint is critical for the diagnosis of periprosthetic joint infections (PJIs) [1], it is not obvious if culture of synovial fluid with a polymethyl methacrylate (PMMA) spacer in place before reimplantation is helpful for the diagnosis of persistent infection [2]. In fact, it has been demonstrated that aspiration for microbial culture before the second stage has a low sensitivity for predicting infection [3–6]. Lonner et al. investigated the role of knee aspiration for detection of persistent infection before reimplantation and after cessation of a four- to eight- week course of antibiotics. They found that knee aspiration performed after resection arthroplasty had a sensitivity of zero, a positive predictive value (PPV) of zero, a negative predictive value (NPV) of 75% and a specificity of 92% [6]. Janz et al. studied the diagnostic performance of synovial aspiration in resected hips without a PMMA spacer, for detection of infection persistence prior to total hip arthroplasty (THA) reimplantation. They found a sensitivity of only 13% and specificity of 98% and concluded that aspiration of a resected hip neither reliably confirmed nor excluded the persistence of infection [5]. Hoell et al. investigated 115 patients with two-stage hip or knee arthroplasty and found that the sensitivity of the aspiration culture before replantation was 5% (95 % confidence interval (CI), 0.13–24.87) and the specificity was 99% (95 % CI, 94.27–99.97). The NPV was 83% and the PPV was 50 % [4]. Preininger et al. investigated the diagnostic validity of synovial PMMA spacer aspiration after two weeks of antibiotic holiday for detection of persistent infection. They included 73 patients who underwent two-stage revision for infection and found only 21% sensitivity for synovial PMMA space aspiration. They concluded that synovial PMMA aspiration cannot be recommended for exclusion of persistent infection [7].

There are some potential explanations for this finding. First of all, it is possible for bacteria to be in a biofilm and remain adherent to cement spacer, which in turn leads to uncertain predictability of culture from aspirations before reimplantation [8–10]. Secondly, the

elution of antibiotics from PMMA into the joint may interfere with isolation of the infecting organism from the joint aspirate. Although major elution of antibiotics from PMMA cement spacer occurs early, there is usually adequate elution of antibiotics at later dates that can interfere with isolation of the infective organism [11,12].

Another controversial aspect of two-stage revision for infection is the role of reimplantation microbiology [13,14]. Hart et al. reviewed 48 patients underwent two-stage revision for infected total knee arthroplasty (TKA). They found 11 (22.9%) positive cultures at the time of reimplantation; seven of them were different from the primary infecting microorganisms. They could not find any relation between the positive reimplantation culture and the outcome [15]. Bejoen et al. review 152 patients with PJI who underwent two-stage revision over a 4-year period. Patients were managed with antibiotic free interval before reimplantation. They found that reimplantaion microbiology was positive in 21 cases (14%) but did not correlate with eventual outcome. The same organism, determined by comparing species and antibiotic susceptibility patterns, was isolated at both excision and reimplantation in four cases (3%). In 10 cases (6%) a different organism was isolated and in 7 cases (5%) reimplantation cultures were positive following negative cultures at the first stage. They could not find any association between positive culture and outcome; however, patients with positive culture at the time of reimplantation received prolonged antibiotics. Overall, 57% of patients with positive reimplantation microbiology received very prolonged (>1 year) antibiotics [14]. Puhto et al. reviewed 107 patients treated with two-stage revision and found 5.2% positive reimplantaion microbiology. Most of the reimplantation cultures were unrelated to organisms cultured at the first stage, which is similar to the results of earlier studies. They treated all patients with positive reimplantation culture as an acute postoperative PJI. The success rate of two-stage revision was not significantly different in patients with positive versus negative microbiology at reimplantation. However, the only case with positive reimplantation culture who failed had the same organisms in both excision and reimplantation [13].

Tan et al. reviewed 267 PJIs (186 knees and 81 hips) treated with two-stage exchange arthroplasty. Here, 33 patients (12.4%) had > = 1 positive culture result at the time of reimplantation. The isolated microorganism at reimplantation was the same as the initial infecting organism in six (18.2%) of the 33 cases. They found that positive intraoperative culture at the time of reimplantation, regardless of the number of positive samples, was independently associated with > 2 times the risk of subsequent treatment failure and earlier reinfection [2]. Akgun et al. reviewed 63 two-stage revision arthroplasties involving 84 THAs and 79 TKAs. They found > = 1 positive culture at the time of reimplantation in 27 patients (16.6%), which was the same initially infection organism in 9 (33%) of them. The risk of the failure of treatment was significantly higher in patients with a positive culture [16].

It seems that the result of culture at the time of reimplantation is related to the outcome of treatment of two-stage exchange arthroplasty. There are several limitations for those studies that implicate reimplantation microbiology do not affect the outcome of two-stage revision for PJI. Firstly, in some studies they found higher rates of failure in patients with positive reimplantation culture, but this finding did not reach statistical significance due to lack of power from the small cohorts available for analysis [13,15]. Secondly, they considered even one positive culture at the time of reimplantation as acute postoperative infection and put the patients on long term antibiotics sometimes longer than a year which makes the success of treatment doubtful [14].

Based on the current evidence, routine cultures during reimplantation should be obtained and relied on. At least four specimens (tissue and fluid) should be taken at second stage surgical reimplantation, using different sterile unused instruments for each sample for subsequent culture. Even single-positive cultures increase the risk of reinfection and failure of treatment and therefore should not be considered as contamination. Patients with positive reimplantation microbiology should receive further antibiotic after reimplantation [2]. Positive culture during reimplantation with the same initial infecting organism or new organisms is independently associated with higher rate of subsequent failure and earlier reinfection [2,16].

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QUESTION 5: Should routine cultures be taken in patients undergoing total joint arthroplasty (TJA) who had a previous open reduction and internal fixation (ORIF) of the same joint (e.g., prior acetabular fracture)?

RECOMMENDATION: Intraoperative cultures should be taken in patients undergoing TJA who have had a prior ORIF of the same joint.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 87%, Disagree: 11%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

TJA in patients with prior ORIF of the affected joint is a common procedure [1]. A subset of these patients undergoes TJA for resulting nonunion, early fixation failure and/or posttraumatic arthritis. TJA after ORIF is commonly referred as conversion arthroplasty and these have been associated with higher complication rates when compared to primary TJA [2–4]. Among those complications, periprosthetic joint infection (PJI) has been identified as one of the causes ranging from 1.6 to as high as 7% [5–7].

The increased risk of PJI in these patients is multifactorial [8]. Studies have identified that any prior surgery to the joint is a risk factor for PJI, both in knees and in hips [9]. Underlying infection has been postulated as one of the reasons ranging in incidence from 11 to 18% [2]. When evaluating TJA candidates with prior ORIF, some authors report that the measurement of preoperative erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) should be performed to identify infections [2]. They conclude that this is an effective method and that efforts should be made to identify and treat underlying infections prior to TJA to reduce the risk of subsequent PJI.

Systemic and local reactions to prior trauma as well as manipulation at the site of arthroplasty may also predispose these patients to infection. Moussa et al. identified positive cultures in 11 hardware cultures out of 21 patients undergoing hardware removal for reasons different from infection, none of these patients had signs of infection [10]. While none of these patients sustained a later infection, none had additional hardware or prosthesis implanted. Positive cultures in clean orthopaedic surgery can range up to 8.3% without correlation with postoperative infection [11]. Again, these patients did not undergo a subsequent TJA. In a different study, Ritter et al. saw that two positive intraoperative cultures at the time of TJA, in patients with prior surgery, develop PJI [12]. They failed to distinguish ORIF only patients and also included in this group failed aseptic TJA.

Performing routine cultures does not come without risk. Cultures are not an inexpensive tool, cost is around $25 U.S. per culture [11]. Depending on how it is collected, there can be different results in the bacterial growth. Chen et al. demonstrated that during the same knee arthroplasty surgery, if the samples are exposed in the operating room, there can be a contamination in the material leading to a false-positive result [13]. Even if there is a positive culture test, it doesn't necessarily indicate an infection.

While intraoperative cultures are not always positive in infected patients, two or more can correlate with a subsequent PJI. Current MusculoSkeletal Infection Society (MSIS) criteria for PJI diagnosis include intraoperative cultures both as major and minor criterion. Therefore, cultures should be included in the workup for possible infection prior to TJA. Literature is consistent in showing that these patients have an increased risk of subsequent PJI given they had a prior surgery on the affected joint.

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QUESTION 6: Is there a role for sonication of implants retrieved during explantation?

RECOMMENDATION: Several studies have demonstrated that sonication of explanted orthopaedic prostheses is a viable method for detecting pathogens, particularly in the setting of culture-negative infections.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Periprosthetic joint infection (PJI) is an uncommon, but devastating, complication following total joint arthroplasty with serious economic implications [1–3]. Since the management of aseptic implant failure differs from that of PJI, accurate diagnosis is critical [2]. One of the greatest challenges in the treatment of PJI remains the identification of the infective organism. Routine cultures are commonly performed for the microbiological diagnosis of PJI, however, these cultures may be falsely negative, which may complicate management [4]. Prior studies have demonstrated synovial fluid culture sensitivities ranging from 43 to 75% and periprosthetic tissue culture sensitivities ranging from 61 to 73% [5]. Culture sensitivity is dependent upon various variables such as prior use of antibiotics, sampling error, inadequate transport and an insufficient number of viable bacteria retrieved [6].

Investigations have shown that PJI is typically caused by microorganisms forming biofilms on implant surfaces [7,8]. Biofilms are complex bacterial communities capable of self-producing a glycocalyx matrix that protects the cells from environmental and antimicrobial threats [7]. Biofilms can be polymicrobial or possess the ability to recruit other species to allow for permanent attachment to the host tissue and the endoprosthetic surface, thereby increasing antibiotic resistance and metabolic cooperation between all involved bacterial species [8]. Accurate microbiological diagnosis, therefore, depends on the effective disruption of biofilms from implant surface using low-intensity sonication for more sensitive PJI diagnosis than the current conventional methods using a periprosthetic tissue or synovial fluid cultures [9–13]. Sonication before the culture of explanted prostheses has also been shown to enhance bacterial growth in culture by dislodging the sessile organisms [14,15].

Review of available literature shows that sonication fluid cultures (SFC) consistently demonstrates increased sensitivity (78.5% to 97%) in the identification of organism without sacrificing the specificity (81% to 98.8%).[9,10,14,16–19] In a study of 331 patients, Trampuz et al. showed the sensitivity of SFC (78.5%) was significantly superior to tissue culture (60.8%) ($p<0.001$) [10]. They had also shown that use of use of SFC (75%) was more sensitive than tissue culture (45%) when the antimicrobial agent was discontinued within 14 days before surgery [10]. In 2017 Rothenberg et al. used MusculoSkeletal Infection Society (MSIS) criteria and found that SFC was more sensitive than synovial fluid or tissue culture (97 vs. 57%) [17]. Janz et al. have also shown that sensitivity and specificity can be further improved to 100% by separating components into multiple sonication fluid cultures [20].

In contrast to the above results, some studies have shown a lower sensitivity with using SFC suggesting the importance of the technique used [21]. It is also suggested that in early PJI cases sonication is not superior to conventional techniques [22]. As with all microbiological diagnostic tests, the sonication procedure could be potentially contaminated during the process and could result in false-positive results [20,23]. Therefore it is essential to define what constitutes positive SFC. Various studies recommended five Colony Forming Units (CFUs) as a cutoff to limit false-positive results [10,17,24].

While positive histology, periprosthetic tissue and SFC are highly predictive of implant failures in patients with PJI, more than 10% of patients with suspected aseptic loosening are misdiagnosed PJI [25]. Unrecognized or occult infection has been implicated in contributing to "aseptic" loosening of joint prostheses [26]. Studies by Holinka et al. and Janz et al. have shown that all endoprosthetic components are colonized in cases of PJI for revision arthroplasties [14,27]. Investigations to optimize pathogen identification are still ongoing. Studies have indicated that polymerase chain reaction (PCR) of sonication fluid is a promising test for microbiological diagnosis of PJI especially in patients who were on antibiotics [22,28–31]. A limitation of PCR is that identification of bacterial DNA does not necessarily confirm the presence of live bacteria [32]. However, the advantage of PCR is its short processing time (<5 hours) and fully automated procedure [33].

Currently, the microbiological diagnosis of PJI remains a challenge because a gold standard protocol has not yet been established. Cultures are commonly performed for the microbiological diagnosis of PJI, but their sensitivity is influenced by various factors as mentioned earlier. Given the overwhelming literature supporting the increased sensitivity of sonicate fluid to identify pathogens relative to conventional methods, and the feasibility of this technique, we conclude that there is a beneficial role regarding the use of sonication for explanted prostheses in the setting of suspected PJI.

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2.5. DIAGNOSIS: REIMPLANTATION

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QUESTION 1: Are the MusculoSkeletal Infection Society (MSIS) and Interntional Consensus Meeting (ICM) criteria valid for decision-making before reimplantation?

RECOMMENDATION: The validity of the MSIS and ICM criteria for determination of the timing of reimplantation is unclear.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

George et al. [1] studied 79 patients undergoing reimplantation and found that MSIS criteria had a high specificity (96%) in predicting persistent infection, though the sensitivity was low (26%). They also found that patients who had positive MSIS criteria were at increased risk for reinfection after reimplantation. Kheir et al. [2] also investigated the MSIS criteria in patients who were undergoing two-stage exchange for periprosthetic joint infection (PJI) and reported a sensitivity of 25% and a specificity of 87% for detecting persistent infection. The authors further investigated the utility of the leucocyte esterase (LE) strip test and found that the LE strip test was positive in 22.2% of culture-positive and 4.4% of culture-negative cases. The LE test was negative in all patients who had not failed at their latest follow-

up, showing a great negative predictive value. In another study of 32 patients undergoing reimplantation, the authors found that the MSIS criteria had a very low sensitivity (0%), though the specificity was high (89%) [18]. Therefore, the MSIS criteria have a limited utility in the setting of reimplantation; nevertheless, it appears to be useful for ruling in infection.

Cultures are an integral part of the MSIS criteria. Multiple studies examining the role of reimplantation microbiology have found that positive cultures were associated with an increased risk for failure [3–10]. Tan et al. [8] reported that the risk of failure due to infection was higher (odds ratio (OR) = 2.5) in those with a positive culture during reimplantation. The study did not show a difference in the reinfection rates between a single and multiple (≥ 2) positive cultures. Although cultures are useful in predicting failure, the results of intraoperative cultures are not available before reimplantation. Prolonged antibiotics are recommended in patients who have positive intraoperative cultures. In a study by Murillo et al. [6], the authors had seven patients with positive intraoperative cultures during reimplantation and treated them all with 6-8 weeks of parenteral antibiotics. Patients were followed for a median of 30 months and none of them had recurrence of infection. The authors concluded that preoperative cultures can help identity patients who can benefit from an additional debridement procedure with spacer exchange. Mont et al. reported that the reinfection rates were lower in patients who underwent an additional debridement procedure if the preoperative cultures were positive prior to reimplantation [11].

Intraoperative frozen sections can help formulate a decision in a timely manner compared to intraoperative cultures. Studies examining the utility of frozen sections have consistently shown that frozen sections had a high specificity and low sensitivity in detecting persistent infection [1,12,13]. Therefore, a positive result should be treated as infection and reimplantation should be delayed, while a negative result may not be able to exclude infection.

Erthrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been widely used to monitor response to treatment. Currently, there is limited evidence to support a specific cut-off for ESR and CRP. Although some studies have reported that both ESR and CRP decrease between the stages of a two-stage exchange protocol in patients with resolution of infection, their corresponding values are often above the MSIS cut-offs even in patients whose infection has clinically being cleared [14–16].

Synovial markers such as white blood cell (WBC) count and polymorphonuclear leukocytes (PMN) % have shown promising results in determination of reimplantation timing, however the optimal cut-off threshold for WBC count might be lower than the MSIS threshold of 3,000 cells/μL [14,15,17].

One of the major concerns with the studies evaluating the MSIS criteria or its components is the lack of a gold standard for diagnosing PJI or determining persistent infection. Most studies have compared the MSIS criteria with failure after reimplantation or the clinical decision to perform a spacer exchange [1,2,18]. However, it is unclear whether failure after reimplantation is an accurate representation of an undetected persistent infection or a newly acquired PJI. In a multicenter study of 92 patients who developed failure after reimplantation, only 32% of the patients had an identical organism at failure suggesting that many patients may be having a new infection rather than a persistent infection [9]. Another limitation of most studies is the presence of missing data [1,2,18]. As diagnostic tests are often performed in patients with an uncertainty in the diagnosis, it is possible that many patients with obvious infection may not have had all the appropriate tests performed. This can underestimate the utility of the MSIS criteria and maybe partly responsible for the low sensitivity of the MSIS criteria.

In summary, very few studies have evaluated the role of MSIS criteria in determining the reimplantation timing. Therefore, it is unclear whether the MSIS or the ICM criteria are a reliable tool for this matter. Cultures constitute a major part of MSIS criteria and a positive culture at reimplantation has been shown to increase the risk of failure in numerous studies. Frozen sections are reported to have a high specificity, though their sensitivity is limited. Synovial markers such as WBC counts, PMN % and the LE test had better results in diagnosing persistent PJIs compared to serum markers. Although ESR and CRP decrease between the stages of a two-stage exchange treatment, they cannot be reliably used to detect persistent infection at the current thresholds. There is a dire need for an accurate diagnostic test to determine optimal timing of reimplantation in patients undergoing surgical treatment for PJI.

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QUESTION 2: What metrics should be considered to determine the timing of reimplantation after two-stage exchange arthroplasty of the infected hip or knee?

RECOMMENDATION: There are no definitive metrics to allow determination of optimal timing of reimplantation. Thus, timing of reimplantation should consider resolution of clinical signs of infection, down-trend in the serological markers and results of synovial analysis, if aspiration is performed.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Because optimal timing for reimplantation is unknown, most surgeons prefer to rely on a combination of clinical evaluations, such as clinical evidence of infection control and normalized laboratory values after a period of antibiotic therapy [1]. There is no gold standard that can guide surgeons to determine the optimal time of reimplantation [2]. Various serum and synovial markers have been studied to identify the most accurate test for screening for persistent periprosthetic joint infection (PJI). A common finding of most of the studies is a high specificity, but low sensitivity.

Serum Analysis

Several serum markers have been evaluated for PJI, but only a few prior to reimplantation. Serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have been widely evaluated for diagnosis, monitoring treatment and evaluating their role in identifying the optimal timing of reimplantation [2–9]. Although a decreasing trend in both markers is seen during the interval period, they can still be elevated in patients that are considered to have a treated infection and have also been seen to be normal in persistent infection. In different studies, no cut-off values could be determined and there were no significant differences in average ESR and/or CRP values at time of reimplantation between infected and non-infected cases [3,7].

Interleukin-6 (IL-6) has been recently studied among other biomarkers in PJI. It has been seen that it may have a role in defining persistent infection prior to reimplantation, although stronger evidence is needed [10]. A recent study by Shahi et al. [11], showed promising results in determining the reimplantation time using serum D-dimer test. In their cohort, 29 patients underwent reimplantation surgery for PJI. Five patients had elevated D-dimer levels at the time of reimplantation, two of which had a positive culture from intraoperative specimens (*Staphylococcus epidermidis* in one patient and *Cutibacterium acnes* (*C. acnes*) in the other patient). Both of those patients subsequently experienced failure due to infection. Based on the results of this study, D-dimer outperforms both ESR and CRP for determining the timing of reimplantation. The corresponding CRP and ESR values were falsely negative in both of these patients (a CRP level of 8 mg/L and an ESR of 20 mm/hr in one patient; a CRP level of 1 mg/L and an ESR of 9 mm/hr in the other patient). Ongoing clinical research is currently investigating the utility of D-dimer in determining the timing of reimplantation surgery. D-dimer is an inexpensive and widely available test that can aid in identifying the timing of reimplantation.

Joint Aspiration

Synovial fluid aspiration and analysis for cell count, microbiological culture and biomarkers prior to reimplantation is also widely being used to detect persistent infection. Studies on synovial fluid WBC and differential analysis are contradictory [6–9,12,13]. Kusuma et al. [7], showed that prior to reimplantation, synovial fluid white blood cell (WBC) and differential analysis are poor markers of persistent PJI in the knee. Conversely, Shukla et al. (6) found pre-reimplantation synovial WBC count to be highly diagnostic of persistent infection in the hip. Zmitowski et al. [12], reported elevated synovial WBC count and polymorphonuclear lukocyctes (PMN)% statistically significant in patients with persistent PJI but did not provided useful threshold to identify patients with persistent PJI. Almost all studies evaluating microbiological culture of joint aspirate report a very low sensitivity, which means persistent infections are not detected [8,9,13,14]. In addition, Mühlhofer et al, [8] identified that microbiological synovial fluid analysis can also be misleading due to false positive cultures.

Kheir et al, [15] reported on the use of the leukocyte esterase (LE) as a screening test for persistent infection. This test demonstrated a high specificity (100%), but low sensitivity (25%). A positive LE result had a high predictive value of failure of reimplantation. Frangiamore et al, [16] evaluated synovial fluid cytokines to determine the highest diagnostic accuracy for PJI. IL-6 and IL-1β showed the greatest decrease between first and second stages; these could potentially be used to monitor PJI treatment response. Due to the low sensitivity of these tests, they fail to provide a definite answer as to the infection status.

MusculoSkeletal Infection Society (MSIS) Criteria

The efficacy of MSIS criteria for determining infection resolution in PJI has also been evaluated [15–17]. Despite the clinical importance of these criteria, the lack of sensitivity of these tests do not make them useful in diagnosing persistent infection. Frangiamore et al. reported a specificity of 89% and sensitivity of 0% for MSIS criteria to rule out PJI after the first-stage [16]. Another study by Georges et al. [17], evaluated 97 patients undergoing reimplantation and also demonstrated a high specificity but low sensitivity for MSIS criteria

for diagnosing persistent infection. They concluded that MSIS criteria should be evaluated at the second stage of revision arthroplasty because they discovered that performing reimplantation in a joint that is MSIS-positive for infection significantly increased the risk for subsequent failure.

Intraoperative Tests

Intraoperative frozen sections have also been used as a reliable indicator of infection during revision arthroplasty. These have been well studied for infection eradication in revision surgeries. Although there is still debate about the optimal diagnostic cut-off (number of PMNs per high-power field), authors have recommended that reimplantation should be delayed when frozen sections are positive. However, intraoperative frozen sections are not reliable enough for ruling out persistent infection because of a low sensitivity [17–21]. Della Valle et al. showed a sensitivity of 25% in their study (18). More recently, George et al. reached a 50% sensitivity, despite the fact that these specimens were evaluated by a highly specialized pathologist [17]. Intraoperative microbiology stains are not recommended due to their very low sensitivity [22–24].

We consider that a combination of available diagnostic variables should be evaluated to determine the infection status of a patient prior to reimplantation. A surgeon must rely on this strategy and clinical judgment to proceed with reimplantation.

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QUESTION 3: Is normalization of serological markers necessary prior to reimplantation arthroplasty performed as part of a two-stage exchange?

RECOMMENDATION: No. A trend and decline in C-reactive protein (CRP) and erthyrocyte sedimentation rate (ESR) is expected, but we still recognize that there are certain cases in which reimplantation may be performed despite abnormal levels of ESR and CRP. Surgeons should not wait for complete normalization of the inflammatory markers as this may not occur in some patients and/or take a long period of time.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Among the efforts to improve the effectiveness of the two-stage exchange for periprosthetic joint infection (PJI) are the attempts to identify persistent infection, by the use of primary and secondary inflammatory markers, before reimplantation.

A decline in ESR and CRP levels in conjunction with the absence of clinical signs of infection are often believed to be an indication that it is safe to proceed with reimplantation. Ghanem et al. [1] demonstrated that in patients with recurrent infection, ESR and CRP mean levels, before the second stage, were similar to those in patients whose infection had been successfully treated. Similarly, Kusuma et al. [2] found no significant difference in test results between the persistently infected and non-infected groups before second-stage surgery. In both studies, the authors constructed a retrospective review with the intent of determining a specific value of ESR, CRP, or both that could be used to detect continued infection prior to reimplantation. They found that no such value could be determined and that the ESR and CRP of those with and without infection were similar.

The persistently elevated ESR and CRP levels, at the time of reimplantation, were found in 54% and 21% of the patients, respectively. Also, Shukla et al. [3] reported that the mean ESR and CRP levels significantly decreased between stages, but remained elevated in 62.5 and 27.5% of the patients in whom the infection had been eradicated.

Kubista et al. [4] found no statistically significant differences in mean values for CRP or ESR before resection or reimplantation when comparing the treatment failure group to the control group.

One study did note that there was a weak trend between the level of inflammatory markers prior to reimplantation and the subsequent outcome in total knee arthroplasty (TKA) patients undergoing two-stage exchange arthroplasty [5]. In a similar study for total hip arthroplasty (THA), no association between successful second stage reimplantation and pre-reimplantation levels of ESR and CRP could be detected [6]. Likewise, the values did not differ between failure and success groups in a series reported by Mortazavi et al. [7]. Therefore, the available evidence suggests that serologic markers cannot be the only factor in guiding the surgeon for the appropriate timing of reimplantation.

While some authors advocate for waiting until normalization of inflammatory markers ESR and CRP [8–11], many others [12–16] rely upon a downward trend of the markers before proceeding with reimplantation. In those cases, in which no constant decrease of the values is observed, some prefer to promote spacer exchange instead of reimplantation [17,18].

The level of inflammatory markers may remain elevated in patients with inflammatory conditions which can cloud the picture [19,20]. The inflammatory markers should still be measured in patients with inflammatory conditions both for the purpose of diagnosis of PJI and also determining the timing of reimplantation. George et al. [21] analyzed the diagnostic utility of ESR and CRP to detect, at the time of the second stage, persistent infection in patients with inflammatory arthritis. At the time of reimplantation, ESR and CRP remained elevated above the MusculoSkeletal Infection Society (MSIS) threshold in many patients with inflammatory arthritis. The authors, however, did conclude that persistently elevated serological markers should not always be presumed to be the result of underlying inflammatory arthritis, and could suggest an ongoing infection [21].

Previous studies have examined the role of other serum markers for infection. One such marker is Interleukin-6 (IL-6) that has been shown to be highly predictive of PJI in patients undergoing revision surgery in one study [22]. A cut-off serum value of 8 pg/ml is a sign of an absence of infection and perhaps an indication for reimplantation. Other studies have not been able to prove value for serum cytokines but have suggested that if such markers are measured a downtrend between the two stages may provide an important guide for clinicians to monitor the treatment response [23]. Recently the serum D-dimer was reported to have a great potential for diagnosis of PJI [24]. The utility of this test for optimal timing of reimplantation is being evaluated and the preliminary results presented in the American Academy of Orthopaedic Surgeons (AAOS) annual meeting, by the same authors, appeared to be encouraging.

Regarding the analysis of synovial fluid, Zmistowski et al. [25] postulated that synovial fluid analysis, even though of unclear utility, may detect persistent PJI before reimplantation. Shukla et al. [3] observed that white blood cell (WBC) count could identify persistent infection with a cut-off value of 3,000 cells/μL. To the contrary, Muhlhofer et al. [26] could not establish cutoff values for CRP, leucocytes, WBC count and polymorphonuclear (PMN) percentage, thereby observing that no reliable markers were indicative of persistence of infection. CRP and leucocytes were often found to be elevated, even when the infection had been controlled.

A synovial biomarker with great promise is leucocyte esterase (LE). A study by Kheir et al. found that a positive LE test (defined as ++) at the time of reimplantation was indicative of persistent infection and predicted a later failure with great accuracy [27]. Another recent study from the same institution by Tarabichi et al. [28] posited that analysis of LE, when used in conjunction with serologic screening, is a powerful point of-care test for diagnosis of PJI and timing of reimplantation. Based on the available evidence it is worthwhile to consider the use of LE strips at the time of reimplantation that can provide the surgeons with additional and definitive analytical information.

Based on the current evidence, serum inflammatory markers, ESR and CRP, are not believed to be reliable on their own in determining the presence of infection. It is our understanding and recommendation that these markers should still be monitored between the two stages and a decline in their value sought before proceeding with reimplantation. The value of the serum ESR and CRP in timing the reimplantation may be improved if the result of synovial fluid analysis, in particular using the LE strip test, and possibly other serum markers, such as D-dimer, are combined. There is a need for future studies to identify the most appropriate marker that may be indicative of persistent infection.

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QUESTION 4: What is the importance of two-week antibiotic holiday prior to reimplantation?

RECOMMENDATION: Unknown. There is no conclusive evidence to support the need or the ideal length of an antibiotic holiday prior to reimplantation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 7%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Two-stage exchange arthroplasty continues to be the preferred method of treatment for chronic periprosthetic joint infections (PJIs) in the United States and Europe. Traditionally, the procedure involves removal of all foreign material and a six-week period of ensuing antibiotic treatment. Prior to reimplantation it is customary to implement a 14-day antibiotic-free interval, known as a drug holiday, intended to allow for "emergence" of residual infection [1]. During this period serological testing and synovial aspiration are usually performed to ensure that infection is under control prior to proceeding with reimplantation. However, this widely implemented therapeutic option has remained controversial [2] because of the paucity of the systemic antibiotic treatment after six weeks, which can lead to the persistence of an infection and the development of multiple drug-resistant bacterial strains.

In addition, the accuracy of serological tests and synovial aspiration under ongoing systemic antibiotic therapy is debatable. Ghanem et al. [3] and Spangehl et al. [4] have reported that data regarding the value of serological markers and synovial aspiration between the stages have been published using heterogeneous cohorts, short follow-up periods and inconsistent antibiotic-free intervals. Meanwhile, some studies have suggested the abandonment of the systemic antibiotic pause after six weeks in favor of a continuous antibiotic administration [5,6].

Bejon [7] et al. (2010) retrospectively reported on 152 patients with periprosthetic joint infection (PJI) who were treated with two-stage revision with a success rate of 83% over a median follow-up duration of 5.7 years; this is within the reported range of success rates [7]. The reimplantation was preceded by a two-week antibiotic-free period in 88% of the cases. However, the microbiology was positive in 3 of 18 patients (16%) without a two-week antibiotic-free period compared with 18 of the 134 patients (13%) with a two-week antibiotic-free period. At reimplantation, more knee joints were culture positive than hip joints, despite being less frequently culture positive at the first-stage excision. Spacers were used in all knee joint revisions; however, they were rarely used for the hips (13%). They did not use aspiration but waited during the two-week antibiotic-free period and decided whether to perform reimplantation based on the clinical appearance. Most unexpected debridements following the first

stage were performed without discontinuing the antibiotics. They concluded that there was no evidence supporting the application of an antibiotic-free period prior to reimplantation and routine reimplantation microbiology. The authors did not find evidence to support the implementation of an antibiotic holiday.

Müllhofer [5] et al. (2018) examined 112 patients who were MusculoSkeletal Infection Society (MSIS) criteria-positive for prosthetic joint infection, including 45 patients with total hip arthroplasties (THAs) and 67 with total knee arthroplasties (TKAs). They treated all patients with a two-stage protocol using a mobile polymethal methacrylate (PMMA) spacer after a 14-day antibiotic-free interval, during which serological markers (C-reactive protein (CRP) and leucocytes) were assessed and synovial aspiration (white blood cell (WBC) count, polymorphonuclear cell (PMN) percentage and microbiological culture) was performed, and the outcomes were compared with those of their long-term follow-up (mean follow-up, 27 months; range, 24 to 36 months). They identified no reliable marker that was suggestive of the long-term persistence of an infection. CRP and leukocytes were often elevated although the infection was controlled. Normalized serum markers did not exclude the persistence of an infection during the follow-up period.

The synovial analysis of WBC count and PMN percentage did not support their well-investigated diagnostic reliability before stage one. The authors pointed out that microbiological synovial fluid analysis was often misleading because of false-positive microbiological cultures, which resulted in overtreatment. In addition, they emphasized the need for high-quality antibiotic treatment, including biofilm-active antibiotics, without any antibiotic holiday for diagnostic reasons. Moreover, they suggested that the reliability of serum markers increases if the time between the first and second stages is prolonged up to 6 months or one year, accounting for a poor functional outcome and increased psychosocial burden [3,5].

In contrast, Janz [8] et al. (2016) have reported remarkably high sensitivity (95%) with low specificity (20%) for serum CRP for predicting the persistence of the infection of resection arthroplasty hips without PMMA spacers. In their study group, the interval between the removal of an implant and the performance of the second stage was up to several months in the Girdlestone-hip group, whereas the cohorts of Müllhofer [5], Kusuma et al. [9] and Ghanem et al. [3] exhibited a standardized timeline with a diagnostic workup eight weeks after explanation.

Boelch [6] et al. (2018) retrospectively analyzed 92 aspirations before the planned joint reconstruction during the two-stage exchange with hip spacers. The PJI was diagnosed according to the Clinical Practice Guidelines by the Infectious Diseases Society of America.

The mean duration from the index surgery to the prosthesis removal was 58.75 months (median, 14.38 months). In the study, 47.8% of the prosthesis removal were primary revisions, and 57.6% patients were males. In addition, the mean age at the prosthesis removal was 67.46 years, and the mean Body Mass Index (BMI) was 29.8 kg/cm^2. An articulating (91.3%) or a resection arthroplasty spacer (8.7%) was implanted at the surgeon's preference. Spacers were molded by hand with a Steinman pin as an endoskeleton. In addition, Palacos R+G and 2 gm of vancomycin per 40 cm^3 of the batch were routinely applied. If preoperative cultures from aspiration exhibited no growth, then antibiotic therapy was initiated in combination with an aminoglycoside and a cephalosporin.

In case of bacterial detection, antibiotic therapy was modified according to a microbiologist's recommendation. In this study, the mean duration of intravenous antibiotic administration was 18.5 days, followed by a course of oral antibiotic therapy for a mean of 17.0 days.

The mean combined duration of antibiotic therapy was 34.4 days, and the mean drug holiday was 15.3 days. Precisely, 72.8% of inter-stage aspirations were performed after a drug holiday of at least 14 days. Aspiration was performed under sterile conditions. Their results implicated that neither the synovial fluid culture nor the synovial leucocyte count at the inter-stage aspiration during the two-stage exchange of the hip with a spacer was consistent as a standard approach for ruling out the persistence of the infection.

Thus, the authors preferred reconstruction or spacer exchange without any cessation of systemic antibiotic therapy, and they strongly discouraged aspiration during the two-stage exchange and instead recommended considering a high CRP before prosthesis removal and reconstruction suggestive of an increased risk of the persistence of an infection. Our literature review highlights that no single factor could be used alone when evaluating the success of two-stage arthroplasty in eliminating infection.

Thus, we must rely on a combination of clinical evaluation, imaging, serologic tests and biopsies to ascertain the timing of reimplantation. Additionally, there seems to be little evidence for deferring reimplantation until all serologic markers are normalized, which, perhaps, can lead to prolonged disability and ultimately cause soft tissue contractures and further bone loss [3].

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QUESTION 5: What is the diagnostic accuracy of joint aspiration of a cement spacer in conjunction with clinical evaluation, imaging, serologic tests, and biopsies? Should it routinely be performed prior to reimplantation?

RECOMMENDATION: The diagnostic accuracy of joint aspiration prior to reimplantation is not known. None of the parameters being used to diagnose periprosthetic joint infection (PJI), and their respective thresholds, have been determined for aspiration. The decision to perform aspiration should be made based on the index of suspicion for persistent infection and individualized.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Until today none of the diagnostic methods for PJI have demonstrated 100% specificity or sensitivity [1]. Therefore, a diagnostic method that involves a combination of clinical evaluation, imaging, serologic tests, as well as aspirate tests and biopsies, needs to be established for confirming the diagnosis of PJI. Two-stage exchange arthroplasty is comparable with one-stage exchange arthroplasty in that all the components are removed at the time of surgery. In contrast to one-stage arthroplasty, in two-stage surgery cases, a temporary antibiotic delivery device (a spacer) is implanted locally, and systemic antibiotics are administered intravenously for four to six weeks, with an antibiotic holiday of two to eight weeks prior to reimplantation for confirming the elimination of the infection [2–4] and to ensure that the samples collected at reimplantation for microbial culture do not give negative results owing to previous antibiotic use [4].

The two-stage reimplantation procedure for managing infected total knee arthroplasty (TKA) was first described by Insall et al. [5] in 1983. According to them, the first stage includes the removal of all the foreign materials from the joint. Thereafter, the debridement of all soft tissues, bone, synovectomy, irrigation and reaming of the medullary canals is performed. After joint preparation, antibiotic-loaded cement beads and/or a static or articulating spacer is inserted, followed by the closure of the soft tissues and the skin. The patient is then prescribed antibiotics for an extended period of time. Intravenous antibiotics are most commonly used and are selected on the basis of the sensitivities of the infecting organisms, as determined from the preoperative and intraoperative microbiologic cultures [5].

In 2000, Mont et al. [6] conducted a prospective study involving 34 patients who had undergone an aspiration before reimplantation, four weeks after antibiotic administration was discontinued. The authors concluded that cultures of knee aspirates had 75% sensitivity, 100% specificity, 100% positive predictive value, and 97% negative predictive value.

Beckerom and Stucky [7] (2006) studied the cultures of aspiration fluid from 68 infected knees in 67 patients; they reported 32 true positives, 17 true negatives, 6 false positives, and 13 false negatives and concluded that preoperative aspiration had a positive predictive value of 71% and a negative predictive value of 74%. They stated that a positive aspiration result may indicate prosthesis infection; however, a negative result does not rule out infection, and one must consider a coagulase-negative Staphylococcus infection in such cases.

Meermans and Haddad [8] (2010) prospectively followed 120 patients with assumed infection of total joint arthroplasty, including 64 with total hip arthroplasties (THAs) and 56 with TKAs. All patients had undergone aspiration with culture and biopsy. They inferred that the sensitivity was 83% for aspiration, 79% for biopsy, and 90% for the combination of both the techniques. The specificity was 100% for aspiration, biopsy and the combination. Their overall accuracies were 84%, 81%, and 90%, respectively. They concluded that routine aspiration should be followed by a biopsy in the workup of septic joints.

Lonner et al. [9] (2001) published a study of 34 infected knee prostheses, where aspiration was performed for the detection of persistent infection prior to reimplantation and after the completion of a four to eight week course of antibiotics. They concluded that knee aspiration following resection arthroplasty had sensitivity and positive predictive value of zero, a negative predictive value of 75%, and a specificity of 92%. They further stated that a negative result of joint aspiration after resection arthroplasty may not necessarily rule out current infection. The average antibiotic-free interval in all patients was 20 days; patients with false-negative results of aspiration had an average antibiotic-free interval of 11.5 days compared with 26 days among all other patients.

In addition, the study performed by Ghanem et al. [10] (2009) reported that a negative result of aspiration of the knee did not rule out infection. They observed false-negative aspiration in 15% of their cases, similar to the report by Lonner [9] et al.

Sanchez-Sotelo et al. [11] (2009) focused on long-term reinfection-free survival and mechanical durability; they retrospectively reviewed 168 patients (169 hips) with infected arthroplasty, all of whom had undergone two-stage reimplantation for an infected THA from 1988 to 1998. In the second stage, the femoral component was fixed with antibiotic-loaded bone cement in 121 hips, while the other femoral components and all the acetabular components were uncemented.

The minimum follow-up time was 2 years (mean, 7 years; range, 2–16 years). At the most recent follow-up, 12 hips (7.1%) had undergone re-operation for reinfection, and 13 hips (7.7%) were revised for aseptic loosening or osteolysis. Aseptic loosening occurred on one or both sides of the joint in 24 hips (14.2%). The 10-year rates for survival without reinfection and mechanical failure were 87.5% and 75.2%, respectively. Nineteen hips dislocated and eight underwent revision surgery for instability. The two-staged procedures included the removal of all the prosthetic components, cement (if present), and all the foreign bodies followed by intravenous antibiotic therapy and delayed reimplantation of THA. They applied a spacer made of antibiotic-loaded polymethyl methacrylate in 31 hips, while the remaining hips underwent resection arthroplasty for the time interval between implant removal and reimplantation.

In the 23 hips with negative intraoperative cultures, infection was diagnosed on the basis of positive intraoperative pathology (13 hips), frank purulence (nine hips, six with positive pathology), positive preoperative aspiration (14 hips, seven with positive pathology)

and/or macroscopic evidence of infection. The average duration of intravenous antibiotic therapy was 6 weeks (range, 3–18 weeks). The median duration of the interval between the resection and reimplantation was 9.4 months (range, 3–18 months). After reimplantation, antibiotics were discontinued when the intraoperative cultures were finalized, except in 16 patients (16 hips) with chronic oral suppression antibiotic therapy.

Kusuma et al. [12] (2011) have determined serology (erythrocyte sedimentation rate (ESR)/C-reactive protein (CRP)) and aspiration (synovial white blood cell (WBC) count) to be predictive parameters for determining the appropriate timing for definitive second-stage reimplantation. These were compared when stopping antibiotic treatment prior to the second-stage procedure. The WBC count in the synovial fluid was found to be the most reliable indicator of infection resolution. However, the researchers were unable to launch any definitive outlines indicative of persistent infection.

Newman et al. [13] retrospectively evaluated 77 hips undergoing aspiration before a second stage reimplantation and found a sensitivity of 30% and specificity of 100% in detecting infection. Similarly, Preininger et al. [14] found that pre-reimplantation aspiration cultures had a high specificity (100%), but low sensitivity (21%).

Although a majority of the studies report a high specificity with respect to cultures, the utility of other aspiration tests is less clear. Shukla et al. [15] found that WBC counts had an area under the curve (AUC) of 0.91 at cut-off of 3,528 cells/μL (sensitivity, 78%; specificity, 96%), whereas polymorphonuclear (PMN) % had an AUC of 0.81 at cut-off of 79% (sensitivity, 78%; specificity, 82%). Newman et al. [13] reported a sensitivity and specificity of 47% and 87% for WBC counts (AUC = 0.67), and 76% and 80% for PMN % (AUC = 0.78), respectively at the MusculoSkeletal Infection Society (MSIS) thresholds of 3,000 cells/μL and 80 PMN %. They also found that when any of the aspiration results were positive for infection (WBC >3,000 cells/μL or PMN % >80 or positive culture), aspiration had a good diagnostic performance (AUC = 0.82). Additionally, they found that lowering the threshold for WBC count significantly improved the diagnostic sensitivity (47 - 76%) while slightly decreasing the specificity (87 - 78%). On the contrary, Hoell et al. [16,17] reported poor diagnostic performances for WBC counts in their two studies (AUCs of 0.37 and 0.56), though the cut-off obtained was close to 1,000 cells/μL. Kheir et al. [18] found that leukocyte esterase (LE) test performed on synovial fluid had a sensitivity and specificity of 26% and 100%, respectively (AUC = 0.56) for detecting persistent infection. They also found that a positive LE test was associated with increased risk of reinfection after the reimplantation surgery.

Most of the studies were performed in a retrospective manner causing an inherent bias in patient selection and were of moderate or low quality [19]. A major concern while interpreting the studies assessing the utility of aspiration is the uncertainty regarding the gold standard test to diagnose persistent infection. Many studies compare the aspiration results to intraoperative cultures, histology or other markers at time of reimplantation, while some studies compare to subsequent failure after reimplantation. Lack of adequate fluid (dry taps) is another concern while performing preoperative aspirations on spacers [13]. Sometimes, saline lavages are performed in an attempt to obtain fluid when such dry taps are encountered. Newman et al. [13] compared the accuracy of aspiration performed with and without a saline lavage, and found that synovial WBC counts and PMN % were noticeably affected by lavage, while culture results were less susceptible to lavage.

In summary, it appears that cultures obtained before the planned second stage are helpful in ruling in persistent infection. A patient with positive culture is likely to benefit from an additional debridement. However, a negative culture does not rule out persistent infection and additional clinical, and laboratory markers should be considered in these patients. WBC counts and PMN % have demonstrated good diagnostic utility, though the WBC cut-off might be lower than the MSIS threshold.

It is well known, that the most important factors in favor of routine aspiration are its reliability, low cost and simplicity of application in an outpatient clinic. Given the studies [8,12] as Level II, diagnostic studies emphasizing the diagnostic accuracy of an aspiration of a cement spacer following a drug-holiday in literature, we conclude that aspiration of a cement spacer in conjunction with clinical evaluation, imaging, serologic tests and biopsies has high diagnostic accuracy and may be performed before reimplantation based on the index of suspicion for persistent infections [20,21].

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QUESTION 6: What intraoperative metrics can be utilized at the time of intended reimplantation to help decision-making and reduce the risk of subsequent recurrence?

RECOMMENDATION: Intraoperatively, frozen section and leukocyte esterase (LE) strip test can be used as decision-making metrics for reimplantation.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 66%, Disagree: 25%, Abstain: 9% (Super Majority, Weak Consensus)

RATIONALE

The intraoperative decision-making process for reimplantation must be based on metrics that are fast (due to time constraints), accurate to reduce the risk of recurrence and reliable so that such metrics can be reproduced in many scenarios.

Frozen Section (FS)

Intraoperative FSs have been used as a fast and accurate indicator of infection during reimplantation due to high specificity. Most of the studies recommend withholding reimplantation in the presence of positive results. Nonetheless there is a debate regarding optimal cutoff for the number of polymorphonuclear cells (PMNs) per high-power field and whether this should be a quantitative or qualitative analysis. The primary reason FS is not universally accepted as a decision-making marker is its reliability. FS continues to have a low sensitivity (between 25 - 50%) in the presence of infection [1–5]. FS is also dependent on a highly specialized pathologist with experience, which is evident in a study published by George et al. where even in the presence of a highly trained pathologist, the sensitivity only reached 50% [5]. Gram and fungal stains have very low sensitivity [6–8], and therefore are not recommended.

Leukocyte Esterase (LE)

The LE strip test has the advantages of being a fast, accurate and reliable test. This is supported by several recently published studies and a meta-analysis [9–22]. These publications show that LE has a sensitivity that ranges from 49% up to 95%, and a specificity that ranges from 82 - 100%. Some papers also have shown a positive predictive value (PPV) from 71.5 to 100%.

One of the limitations observed with LE, being a colorimetric assay, was the potential for inaccurate readings in the presence of a bloody sample. A recent study by Li X et al. [23] showed that when a bloody sample is centrifuged, the LE continues to have excellent sensitivity and specificity (92 and 93.1% respectively), making it still a very reliable test for intraoperative decision-making. Another concern when LE started to be widely used was its accuracy in the presence of adverse local tissue reactions (ALTR), namely metallosis. Tischler et al. [12] demonstrated that LE combined with PMN % was reliable in ruling out infection in 92.9% of the cases evaluated.

Alpha-Defensin

The alpha-defensin test as a reliable synovial biomarker for the diagnosis of infection was introduced by Deirmengian et al. [14] Since then, newer techniques have been developed which achieve similar results in a faster fashion. Alpha-defensin lateral-flow immunoassays [24–31]are faster and have a sensitivity that ranges from 64.7 - 94.5%, a specificity with a range of 87 - 99.6%, a positive predictive value (PPV) from 74.6 - 98.1%, and a negative predictive value (NPV) from 83.7 - 98.2%. However, a few studies [29,30] have demonstrated that the immunoassay test performed in the laboratory setting is more accurate than the lateral-flow technique, and provides sensitivity ranges from 83.6 - 97.1%, specificity ranges of 97 - 100%, PPV ranges from 94.9 - 100%, and NPV ranges from 89.9 - 98.2%.

As with LE, other factors can impact the accuracy of Alpha-defensin testing. The specificity and PPV can decrease in the presence of ALTR [24] and crystal deposition arthroplasties [31].

Interleukins

Another lateral-flow immunoassay technique being used for the diagnosis of PJI involves interleukins, specifically Interleukin-6 (IL-6). This intraoperative test allows for a rapid assessment of the cytokines within the synovial fluid. This technique is already in use with an acceptable specificity but relatively low sensitivity. However, when IL-6 is measured in the lab with radioimmunoassay techniques, it is more accurate [32].

Despite having these time-tested and novel techniques, the surgeon continues to rely on a combination of preoperative testing, intraoperative clinical judgment and the interpretation of these intraoperative metrics to decide whether it is safe to proceed with reimplantation and avoid the risk of PJI recurrence.

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QUESTION 7: What is the diagnostic accuracy of a frozen section (FS) during reimplantation surgery? What thresholds should be used in this context?

RECOMMENDATION: Adequate peer-reviewed literature exists to support either of two diagnostic thresholds for supporting the diagnosis of periprosthetic infections of the hip and knee: 5 neutrophils (PMNs) in each of at least 5 high power (400X) microscopic fields (HPF), or 10 PMNs in each of at least 5 HPFs.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 83%, Disagree: 10%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

A common method of treating periprosthetic infection of the hip or knee is two-stage exchange [1], but it can be difficult to determine if and when the infection has been adequately treated and the infected joint is ready to receive a new implant. The tests commonly used to help diagnose infection at revision arthroplasty, such as serologic tests, microbiologic culture, and the cell count with differential of aspirated joint fluid may have been influenced by the previous surgery as well as an antibiotic-containing spacer and may not have the same predictive value as when they are applied at revision arthroplasty [2].

One of the few tests that can be performed during a reimplantation or revision arthroplasty operation is the interpretation of a FS of

TABLE 1. Study results showing similar values as reported for frozen sections obtained at primary arthroplasty

Reference	Cases	Sensitivity	Specificity	PPV	NPV	Accuracy
[10]*	64	25%	98%	50%	95%	94%
[11]**	79	50%	94%	50%	94%	90%
[13] (FS)**	47	56%	95%	73%	97%	87%
[13] (PS)**	47	89%	94%	80%	97%	94%

PPV, Positive Predictive Value; NPV, Negative Predictive Value; FS, Frozen Sections; PS, Permanent Sections

* Threshold: 10 PMN in each of at least 5 HPF

** Threshold: 5 PMN in each of at least 3 HPF

periprosthetic tissue. In that context, the presence of acute inflammation, as characterized by neutrophils (neutrophilic granulocytes, polymorphonuclear leukocytes, (PMNs), suggests ongoing infection [3-6]. The tissue block from which that section was prepared is then formalin fixed and processed, along with additional tissue samples as a "permanent section" to be interpreted a day or two later. As a rule, the higher the tissue concentration of neutrophils, the more likely the joint is infected, but there is controversy about the best threshold to help diagnose or rule out infection. Several systematic reviews have identified adequate high-quality studies support thresholds of either 5 or more neutrophils in each of 5 HPFs or 10 or more neutrophils in each of 5 HPFs to support the diagnosis of infection [3,7] at the time of revision arthroplasty. Several other thresholds have also been suggested [8,9] and the results of FS have also shown good correlation with the modified MusculoSkeletal Infection Society (MSIS) criteria for periprosthetic infection [4]. However, few studies have addressed the accuracy of FSs to diagnose persistent infection at the second stage reimplantation of a two-stage revision arthroplasty for known periprosthetic infection.

In 1999, Della Valle et al. [10] published a retrospective study of 64 patients (33 women and 31 men) who had undergone resection arthroplasty for periprosthetic infections and from whom FSs were obtained. The resection arthroplasties had been obtained a mean 40 months after arthroplasty and reimplantation occurred on average 19 weeks later. The threshold for suggesting infection was 10 PMNs in each of at least 5 HPF. Cases with fewer than 5 PMN in each of 5 HPF were interpreted as negative. None of the cases had more than 5 but less than 10 PMNs per HPF. As is common practice in pathology, microscopic fields represented areas of maximum neutrophil concentration, not the overall average of the entire section. Of the 64 patients, two had positive FSs, but one was negative on review of permanent sections. 61 of the 62 patients with negative FSs were also negative on review of permanent sections. Four patients were considered to be infected; the remaining 60 patients had negative cultures and histology. The results are summarized in Table I and indicate 25% sensitivity (the FS detected one of four persistent infections), 98% specificity, 50% positive predictive value (PPV), 95% negative predictive value (NPV) and 94% accuracy.

George et al. published two retrospective studies testing the use of FSs and permanent histology to diagnose infection at reimplantation. The first [11] sought to compare the diagnostic accuracy of FSs compared with the MSIS criteria of infection [12] and to further test the use of FS and MSIS criteria to predict clinical failure of reimplantation. The study identified 79 patients who had undergone two-stage revision for infected arthroplasty (38 knees and 41 hips) and had adequate records to assess MSIS criteria, had FS results and minimum 1-year follow-up. Patients had undergone the second step of the two-stage procedure after at least six weeks of antibiotics, and intraoperative samples at the time of reimplantation had been obtained for histologic and microbiologic evaluation. There were 48 men and 31 women. The threshold for interpreting a FS as supporting infection included 5 or more PMNs in 3 or more, 400X high power fields (based on fields with maximum PMN concentration). Note that this threshold requires fewer fields than commonly recommended, so might be expected to have greater sensitivity but less specificity than if 5 or more HPF were required. The FS results were compared to the reference standard, which for this part of the study was the based on the MSIS criteria. The results showed sensitivity of 56%, specificity of 94%, PPV of 50%, NPV of 94% and 90% accuracy (Table I).

Recognizing that rheumatoid arthritis might complicate the interpretation of serologic and other tests for infection at reimplantation, George and co-authors also reviewed the utility of Fss and permanent histology to diagnose infection at reimplantation in patients with an underlying inflammatory arthropathy [13]. They identified 47 revisions (39 patients) with confirmed inflammatory arthropathy, and compared the results of FS interpretation, and interpretation of corresponding permanent sections with the presence or absence of persistent infection as defined by the MSIS criteria at the planned second stage re-implantation. The threshold for positive histology was the same as in their previous study: 5 or more PMN in at least 3 HPF. The results of FS showed sensitivity of 56%, specificity of 95%, PPV of 73%, NPV of 97% and 87% accuracy. Of the 120 specimens analyzed by frozen and permanent sections, there were only four discrepancies. In each, the permanent section was interpreted as positive (infected) while the FS had been interpreted as negative, although not all of these were clinically relevant because some cases had other positive Fss. Ultimately the permanent sections had two false positive results and one false negative, while the FSs had two false positives and four false negatives. Therefore, the results of permanent sections were sensitivity of 89%, specificity of 94%, PPV of 80%, NPV of 97% and accuracy of 94% (Table I).

Although reported results are variable, most studies have indicated that the interpretation of a FS at revision arthroplasty has good NPV (i.e., absent neutrophils supports the absence of infection) [10], but that observation is dependent in part on sampling. In 2010, a Practice Guidelines Committee of the American Academy of Orthopaedic Surgeons (AAOS) found adequate high-quality published literature to support either of two diagnostic thresholds: 5 neutrophils in each of 5 HPFs (of maximum tissue concentration), or 10 neutrophils in each of 5HPFs [14]. A lower threshold for neutrophil concentration would be expected to be associated with increased sensitivity and lower specificity (increased false positive diagnoses [15]. Although most studies have shown the sensitivity of the two thresholds to be equivalent, some studies have reported slightly higher specificity if 10 neutrophils are required rather than 5 [16]. Recognizing that no test has perfect specificity and sensitivity, the

clinical importance of recognizing periprosthetic infection is high enough that some surgeons prefer maximizing sensitivity even at a slight cost of specificity. For example, Kwiecen et al. [4] recently reported sensitivity of 73.7% and specificity of 98.8% for a FS obtained at hip and knee arthroplasty using a threshold of 5 neutrophils in only 3 or more HRFs (the same threshold used in both studies by George et al. described above).

As noted above, the thresholds used to support the presence or absence of periprosthetic infection have been reported mostly from specimens obtained at intended primary revision arthroplasty. Patients with known periprosthetic infection are often treated with the two-stage procedure and it is thought that the surgery and presence of an antibiotic-containing spacer may alter the results of tests commonly used to diagnose infection, including serologic markers, joint aspiration with cell count, microbiologic cultures and possibly histology [2,17,18]. Although few published studies have included enough information to document sensitivity and specificity of different diagnostic thresholds for recognizing persistent infection at the second-stage of a two-stage operation for known infection, the results summarized here show similar values as those reported for FSs obtained at primary arthroplasty. Additional studies, including the use of special stains and rapid molecular tests are needed to help document either persistent infection or adequate resolution of the infection at the time of reimplantation.

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QUESTION 8: Should patients with periprosthetic joint infections (PJIs) caused by Mycobacterium tuberculosis (TB) undergo the typical two-week antimicrobial holiday prior to reimplantation?

RECOMMENDATION: There is no evidence supporting the two-week antimicrobial holiday before reimplantation. Patients with PJIs caused by TB do not need to have the two-week drug holiday.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 88%, Disagree: 6%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

TB is a rare cause of PJIs for which management is not clearly standardized [1,2]. This may be due to the little clinical suspicion and the difficulty in diagnosing this entity [3]. Literature reflects this infrequency with very few publications, the majority being case reports [2,4–14]. McCullough et al. [14] were the first to describe a prosthetic joint involvement due to TB. They hypothesized that this occurred during a bacteremic state following reactivation of latent tuberculosis. This and other reports have shown infection control can be achieved after surgical and pharmacological treatment although no conclusions can be made as to formal and standardization of treatment.

It is important to note that in the majority of publications, treatment is mainly focused on anti-TB chemotherapy associated with surgical intervention with or without removal of the prosthesis. Surgical treatment has been seen to be controversial and sometimes not performed [9]. Pharmacological management has been similar to that administered in extra-articular TB involvement. The literature contains only one systematic review, which included 15 patients, all of whom received 2- to 4-anti-TB chemotherapy agents (rifampin (RMP), isoniazid (INH), ethambutol (EMB) and pyrazinamide (PZA)) for at least six months (range 6 to 24 months) after diagnosis [7]. Thirty-three percent of patients (5 of 15) underwent surgical treatment including debridement and retention of the arthroplasty, while 20% (3 of 15) underwent staged revision arthroplasty, for which the anti-TB chemotherapy was continued at the time to reimplantation [10,11]. According to the latest publication which also included 66 patients, medical treatment with anti-TB chemotherapy varied from 4 to 39 months, as well as in type and number of drugs [13]. However, 56.1% of patients (37 of 66) received at least 12-month treatment. Surgical treatment ranged from debridement 17% (11 of 66), debridement & polyethylene exchange 8% (5 of 66), two-stage exchange 23% (15 of 66) to removal of prosthesis followed by arthrodesis 33% (22 of 66).

The anti-TB chemotherapy, along with surgical intervention, seems to be necessary for management of PJI caused by TB. The ideal duration of antibiotic treatment for these patients is not known, but most believe that at least four months of treatment should be instituted for patients with TB PJI. In addition, it is critical to ensure that patients with PJI caused by TB have no extra-articular nidus for infection. Given the fact that TB PJI could be considered a chronic condition, we consider that any strategy towards assuring infection control or eradication should be attempted.

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Pathogen Factors

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QUESTION 1: Does the virulence (low or high) of the infecting organism affect the treatment of acute hematogenous or chronic periprosthetic joint infections (PJIs)?

RECOMMENDATION: There is currently no evidence showing that the virulence of an infecting organism affects the treatment of acute hematogenous or chronic PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 69%, Disagree: 27%, Abstain: 4% (Super Majority, Weak Consensus)

RATIONALE

Pathogenicity is the ability of an agent to cause disease. The degree to which a pathogenic microorganism can cause an infectious disease is determined by its virulence. Several factors determine the virulence of bacteria, such as the bacterial capsule, presence of adhesin proteins, degradative enzymes, toxins and mechanisms for escaping elimination by host defenses (e.g., intracellular invasion and survival or production of biofilm). In addition, the host susceptibility to an infection also depends on its immune status and the presence of foreign material [1]. The type of virulence factor(s) expressed participate in the clinical presentation of disease. In general, microorganisms that are considered highly virulent tend to cause acute infections (e.g., *Staphylococcus aureus*, streptococci or gram-negative bacilli (GNB)) [2]. In contrast, pathogens with lower virulency are associated with chronic infections (e.g., *Cutibacterium acnes* (*C. acnes*), *Staphylococcus epidermidis* and other coagulase negative staphylococci (CoNS)) [2]. However, whether all virulence factors of a bacterium become expressed and to which degree, greatly depends upon the presence of specific environmental stimuli [3]. For this reason, we will address this question in two ways; 1) we evaluated whether the difference in virulency between different microorganisms (e.g., classically highly virulent microorganisms versus low virulence microorganisms) affect treatment outcome, and 2) we evaluated whether the degree of virulency factors expressed within one species affect treatment outcome.

Degree of Virulency between Different Microorganisms and its Relation to Outcome

A PubMed search was performed for late acute/hematogenous PJIs and chronic PJIs in relation to treatment outcome. All relevant articles were screened for inclusion and references were checked for additional articles. The total number of patients was counted in both groups and a success rate for all patients was calculated (Table 1) [4–19]. For late acute PJIs, 16 studies were included. Of 948 patients, the success rate with a debridement, antibiotics and implant retention (DAIR) procedure was 56% (range 35 to 94%). For chronic PJIs, one meta-analysis (including 62 studies) and 6 published studies thereafter were included [19–25]. Of 4,570 patients with chronic PJIs, treatment success rate was found to be 90% (range 87 - 100%) with one-stage or two-stage exchange procedures.

The outcome of acute and chronic infections is influenced by many factors, with the greatest difference being the surgical strategy used for acute versus chronic PJI—exchange versus no exchange of the prosthesis respectively. Due to the heterogeneity in treatment methods, it is not possible to conclude whether the worse outcomes observed in acute infections are due to the virulence of the bacteria. There are few studies that evaluate high versus low virulence microorganisms using the same surgical approach. Fink et al. studied 39 patients with early PJIs and 28 patients with acute hematogenous infections all of which were treated with DAIR and followed for a minimum of two years in order to investigate the success rate in infection eradication [27]. There was no difference in outcomes between infection caused by higher virulence pathogens (*S. aureus*, Streptococci, Enterococci, GNB) when compared to lesser virulence pathogens (CoNS and anaerobes such as *C. acnes*) [27].

Other authors have also compared the outcomes between *S. aureus* and CoNS PJIs. One study retrospectively examined chronic PJIs treated with suppressive antibiotic therapy [28], while another investigated the outcome of *S. aureus* PJIs versus CoNS PJIs treated with one- or two-stage revision [29]. Acute hematogenous and early PJI treated with DAIR and chronic knee PJI treated with different surgical modalities has also been examined in the literature. None of these studies found a significant difference in success rate after a minimum follow-up of 3 to 24 months [4,5,13–16]. Some authors have even described a worse outcome in patients with PJI caused by CoNS [4]. These findings suggest that virulence is not a risk factor for worse outcomes in PJI.

There are some observational studies that propose that *Staphylococcus* species are associated with recurrence or persistence of infection, due to the high capacity to form biofilms observed within this genus [30–32]. Others have suggested that *S. aureus* in particular is associated with a worse outcome than other microorganisms in general after DAIR [5,6,33,34] as well as after two-stage revision [35]. However, other studies do not observe any significant differences in outcomes of staphylococcal infections in general [36][37][38].

Degree of Virulence within the Same Species and its Relation to Outcome

Environmental stimuli play a large role in the phenotypic expression of virulence factors [3]. For example, it has been demonstrated that the amount of magnesium present in the environment of *S. aureus* determines the down or up regulation of specific virulence genes [15]. The resulting phenotypes have been shown

TABLE 1. Late acute/hematogenous PJI treated with DAIR

Article, Year	N	Success Rate	Comments
Wouthuyzen-Bakker 2018 [26]	340	55%	Unpublished data
Lora-Tamayo 2017 [7]	242	59%	Only streptococci
Akgün 2017 [8]	16	69%	Only streptococci
Tande 2016 [9]	35	74%	Only *S. aureus* bacteremia, 2y survival 62%
He 2016 [10]	11	82%	
Koh 2015 [11]	20	55%	
Holmberg2015 [13]	12	75%	
Puhto 2015 [12]	35	46%	
Koningsberg 2014 [5]	42	76%	
Geurts 2013 [14]	6	83%	
Lora-Tamayo 2013 [15]	52	35%	Only Staphylococci
Kuiper 2013 [4]	32	59%	
Rodriguez 2010 [16]	50	48%	
Byren 2009 [6]	12	83%	Only hips
Giulieri 2004 [17]	27	78%	
Everts 2004 [18]	16	94%	Only streptococci, only 1 patient had formal microbiological cure
TOTAL	**948**	**56%**	

TABLE 2. Chronic PJI treated with One-stage or Two-stage Exchange

Article, Year	N	Success Rate	Comments
Beswick 2014 [19]	4,197	90%	Meta-analysis comprising 62 studies with one-or two-stage exchange. Subanalysis of 11 studies with 1225 patients and only one-stage: success 91.4%
Singer2012 [21]	63	95%	Only 1st. exchange for TKA
Jenny 2013 [22]	47	87%	Only 1st. exchange for TKA
Haddad 2015 [23]	28	100%	Only 1st. exchange for TKA
Tibrewal 2014 [24]	50	98%	Only 1st. exchange for TKA
Zahar2016 [20]	70	93%	Only 1st. exchange for TKA
Gooding 2011 [25]	115	88%	2-step exchange for TKA
TOTAL	**4570**	**90%**	

to be associated with different infection outcomes in a murine model [15]. In addition, there is much debate over which virulence determinants of *S. aureus* are primarily responsible for infection severity in osteomyelitis [4,14,16]. Although some studies identified virulence determinants or bacterial strains involved in bone and joint infections [6,13,16,17], few evaluated whether the presence or absence of these virulence factors in PJI determine treatment outcome [6,17,18].

The literature search revealed three studies that examined the virulence within one species in relation to clinical outcome [4,15,16]. Tande et al. evaluated the outcome of PJIs caused by staphylococcal small colony variants (SCV), a phenotype that has been associated with intracellular persistence and biofilm formation [28]. Despite the general hypothesis that this phenotype is responsible for persistent and relapsing infections, treatment failure was 23.7% in staphylococcal PJIs caused by SCV compared to 30.7% failure in staphylococcal PJI with a normal phenotype ($p = 0.51$) resulting in a hazard ratio of 0.78 (confidence interval (CI), 0.36-1.69) [28]. The second study performed by Post et al. observed a clear relation between the degree of biofilm formation of *S. epidermidis* strains and clinical outcome in 104 patients with orthopaedic device related infections [39]. Weak biofilm formation was associated with a cure rate of 82%, while the formation of a strong biofilm was associated with a cure rate of 66.7% [39]. This difference however was not statistically significant. Strong biofilm formers were primarily observed to possess the of *icaA* gene (intracellular adhesion protein associated with biofilm formation) but the presence or absence of the gene itself was not related to clinical outcome [39]. In contrast, the presence of the gene *bhp* (cell-wall associated biofilm gene) was related to clinical failure, but only in infections of the lower extremity ($p = 0.023$) [39]. Morgenstern et al. conducted a similar study, however they found no statistically significant relationship between *S epidermidis* biofilm forming capabilities and cure rate ($p = 0.076$) [40].

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QUESTION 2: Is there a difference in the treatment outcome for periprosthetic joint infections (PJIs) caused by a single organism and a polymicrobial PJI?

RECOMMENDATION: Polymicrobial PJIs demonstrate inferior treatment outcomes when compared to monomicrobial PJIs. This finding is true for both patients treated with irrigation and debridement and two-stage exchange arthroplasty.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 97%, Disagree: 3%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

PJIs are not uncommon with a reported rate between 6 and 37% [1–4]. Although common organisms such as *Staphylococcus aureus* are commonly isolated in these infections, more virulent organisms such as Enterococcus species, gram-negative bacilli, methicillin-resistant *Staphylococcus aureus* (MRSA) and anaerobic bacteria are more commonly associated with polymicrobial rather than monomicrobial infections [5]. Despite the relative frequency of polymicrobial PJI, there is minimal literature regarding treatment outcomes of polymicrobial PJIs and how they compare to monomicrobial PJIs.

The literature demonstrates that polymicrobial PJIs have inferior outcomes when compared to monomicrobial PJIs. Tan et al. demonstrated that patients with polymicrobial PJI had a higher failure rate (50.5%) compared with monomicrobial (31.5%) and a higher rate of amputation (odds ratio (OR) 3.80, 95% confidence interval (CI), 1.34-10.80), arthrodesis (OR 11.06, 95% CI, 1.27-96.00), and mortality (OR 7.88, 95% CI, 1.60-38.67) compared with patients with monomicrobial PJI [6]. Similarly, Wimmer *et al.* demonstrated that the infection free rate after two years was 67.6 % for polymicrobial infections vs. 87.5 % for monomicrobial infections in a series of 77 polymicrobial PJIs [7]. Furthermore, Marculescu *et al.* demonstrated that the two-year cumulative probability of success of polymicrobial PJIs was 63.8% (95% CI, 43.8%–80.5%) and of monomicrobial PJIs was 72.8% (95% CI, 63%–80.9%). However, this difference was not significant.

The outcomes appear to be poor for polymicrobial PJI regardless of surgical treatment. Tan *et al.* demonstrated that the infection free survivorship for polymicrobial PJI was 55.4%, 49.3% and 49.3% for the two-stage exchanges and 43.2, 43.2 and 38.4% for irrigation and debridement (I&D) at 2, 5 and 10 years [6]. Although this result was not statistically significant, there was a trend towards higher treatment success (p = 0.164) for two-stage exchange arthroplasty. In Marculescu et al., the 2-year survival free of treatment failure for polymicrobial PJIs was 77.7% and 52.7% compared to 83.9 and 54% for monomicrobial PJI for, two-stage exchange arthroplasty and I&D, respectively. This rate was higher but not, statistically significantly different than of polymicrobial PJI treated with similar surgical modalities (p = 0.24 and p = 0.64) [5]. Bozhkova et al. also revealed that treatment success after the first stage of the two-stage procedure was considerably higher (74.8 %, $n = 101$) in patients with monomicrobial infection, compared to only 27.8 % ($n = 15$) in the polymicrobial group ($p < 0.0001$). [8] Furthermore, they found that gram negative PJIs in polymicrobial PJI were associated with failure as the proportion of polymicrobial PJI caused by gram-negative pathogens was 61.5 % in patients with recurrent infection and only 26.7 % in patients with treatment success (p = 0.03). According to data of Tornero et al., for I&D and retention of the prosthesis polymicrobial infection was significantly associated with failure in the global cohort (59.3% vs. 40.7%, p = 0.036) [9]. Only one study did not show the difference between outcome of polymicrobial and monomicrobial PJI [10]. However, this can be explained by insufficient number of PJI cases (only 15 cases) and pathogen properties (*Cutibacterium acnes* (*C. acnes*) in isolation or together with coagulase-negative staphylococci).

There are several explanations for the increased rate of failure in patients with polymicrobial PJIs. One factor is that drainage and the presence of a soft tissue defect have been found to be associated with polymicrobial PJIs [5,6]. Another is that polymicrobial PJIs are associated with organisms that are difficult to treat such as enterococcus and gram negatives [5,6,11] that have been associated with worse outcomes [12,13]. In addition, several studies have demonstrated that patients with polymicrobial PJIs have increased comorbidities and are older than patients with monomicrobial PJIs [5,6], which likely affects their ability to eradicate an infection.

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QUESTION 3: Is there a difference in the type of pathogens that can cause surgical site infections/periprosthetic joint infections (SSIs/PJIs) between hip and knee arthroplasty?

RECOMMENDATION: There is limited evidence to support a difference in the organism profile causing SSIs and PJIs between hip and knee arthroplasty. Isolated studies have reported an increased prevalence of *Streptococcal* and culture-negative PJI around the knee, whereas, *Staphylococcal, Enterococcal, Pseudomonal* PJIs may be more prevalent around the hip. Further work regarding the different flora in these respective body regions is needed, as it may determine antibiotic selection.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Several studies have investigated the profile of organisms causing SSI and PJI following orthopaedic procedures with varying results. *Staphylococci* species are the most commonly isolated agents in orthopaedic prosthetic infections. According to recent literature, these pathogens are the primary source of up to 72% of infections [5–8]. Bacterial resistance has become a significant problem with certain studies reporting up to 27% of PJI are caused by methicillin-resistant organisms [9,10]. The prevalence of resistance also appears to be rising [11].

The published literature depicts *Staphylococcus aureus* (*S. aureus*) as the leading cause of PJI after total joint arthroplasty (TJA) [7,12,13]. A 14-year study evaluating the microbiological profile of PJI after two-stage revision from 1998-2011 found increased infection rates of methicillin-resistant *S.aureus* (MRSA), *Cutibacterium acnes* (*C. acnes*) and *Streptococcus viridans* (*S. viridans*) with no change in gram-negative, gram-positive or fungal infections [14]. Another study investigating 121 patients diagnosed with PJI after total knee arthroplasty (TKA) identified an increase in the prevalence of coagulase-negative *Staphylococcus* (CoNS) between 1994 and 2008, while *S. aureus* appeared to decrease [15]. A separate study conducted by Uçkay et al. evaluated resistance in CoNS orthopaedic infection over a 13-year period and did not identify any change in methicillin-resistance rates associated with CoNS [16].

Aggarwal et al. identified two different organism profiles when comparing 772 cases of PJI from the Rothman Institute in the United States (US) to 898 cases at HELIOS ENDO-Klinik, Hamburg in Europe [12]. The center in Europe had fewer *S.aureus* infections (13.0% vs. 31.0%), but more CoNS PJI than the US site (39.3 vs. 20.2%). There was also a significantly higher incidence of MRSA at the US center (48.1 vs. 12.8%; $p<0.0001$). However, there appears to be conflicting evidence regarding increasing prevalence of resistance in PJI [11].

The incidence of PJI affecting TKA versus total hip arthroplasty (THA) has been estimated at 1-3% and 0.3-2%, respectively [12–14]. Several studies have examined the organism profile causing PJI after arthroplasty, but few have identified any significant difference in profile between hip and knee arthroplasty.

Pulido et al. noted a higher rate of PJI in patients undergoing TKA (1.1%; 48 of 4185) compared to THA (0.3%; 15 of 5060; $p<0.0001$) [13]. A 14-year study identified a linear increase in MRSA, *S.viridans*, and *C.acnes* causing PJI after arthroplasty from 1998 to 2011. However, they identified no difference between organisms causing PJI in TKA and THA ($p> 0.05$) [14]. *Enterococcus* was found in the majority of THA (68%), but was not considered significant after a Bonferroni correction was performed comparing THA and TKA [14].

In a large multi-institutional study evaluating the organism profile causing PJI at two different academic centers, it was found that knees had more culture-negative infections at one of the two centers compared to hips. However, there were no other significant differences in organism profile when comparing hips and knees [12]. Drago et al. evaluated the organism profile and antibiotic susceptibilities of 429 patients diagnosed with PJI from 2013 to 2015 including 229 knee and 200 hip infections. Again, the authors found no difference in pathogen profile between hips and knees. *Staphylococci* were still the predominant organism affecting hips and knees followed by *Enterobacteriaceae* and *C.acnes*. However, methicillin resistance in CoNS was twice as prevalent around the knee versus the hip. Increased resistance to glycopeptides and fluoroquinolones was also observed around the knee in comparison to the hip [17]. Future

studies should aim to further investigate these potential differences in the organism and resistance profiles in hips and knees diagnosed with SSI and PJI.

Groff *et al.* recently examined 1,214 PJI cases (501 hips and 713 knees) over a 17-year timeframe and found significant differences in pathogens causing PJI in the hip and the knee. A higher incidence of *Streptococcal* species (odds ratio (OR) 1.82, 95% confidence interval (CI), 1.23-2.67) and culture-negative PJI (OR 1.53, 95% CI, 1.12-2.09) were identified in TKA compared to THA. In contrast, *Pseudomonas* (OR 2.123, 95% CI, 1.04-4.34), *Enterococcus* (OR 1.72, 95% CI, 1.03-2.86), resistant species (OR 1.64, 95% CI, 1.19-2.25), *Staphylococcus aureus* (OR 1.40, 95% CI, 1.11-1.77) and gram-positive (OR1.37, 95% CI, 1.05-1.78) organisms were more prevalent in hips. The authors suggested that the higher rates of urogenital-associated pathogens causing PJI in hips may have been related to the close proximity of the incision to the flexural creases and the groin region.

Although most studies have not demonstrated a definitive difference in organism profile between hips and knees, some have identified differences in virulence patterns, culture-negative rates, urogenital and fecal bacteria, as well as the overall rates of PJI in bilateral compared to unilateral TKA [12–14,17]. It is important to further delineate the differences in organism profile at these anatomic sites in order to establish adequate protocols and select antimicrobials accordingly, that may account for potential differences in the pathogenic flora and mitigate the risk of SSI/PJI.

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QUESTION 4: Is there a difference in the organism profile that causes periprosthetic joint infections (PJIs) in different countries?

RECOMMENDATION: Yes, there is a difference in the organism profile causing PJIs in different countries and regions of this world. There seems to be a higher incidence of PJI caused by methicillin-resistant *Staphylococcus aureus* (MRSA) in the United States and Australia compared to Europe.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

General strategies to prevent occurrence of PJIs have become more relevant over the last few years. As one recommendation of the International Consensus Meeting on Periprosthetic Joint Infection in 2013, surgical antibiotic prophylaxis with either single or 24-hour dose of cephalosporin should be performed. However, antibiotics (prophylactic and therapeutic) should be selected to cover the most frequently encountered pathogens, which might vary regionally, nationally and internationally (and could be affected as well by other factors) and not simply be administered empirically.

To date, several authors have described the bacterial incidence in isolated series of PJI with either single- or multicenter studies. However, the comparison of organism profiles causing PJI between countries or world regions has been evaluated by relatively few studies.

A study comparing organism profiles between PJI referral centers in the United States (US) (Rothman Institute) and Europe (HELIOS ENDO-Klinik) found that the percentage of MRSA pathogens was significantly higher in the US than in Europe [1]. In addi-

tion, a higher incidence of more virulent organisms was found in the US patient cohort in this study. Stefansdottir et al. and Phillips et al. in their study also found a higher incidence of coagulase-negative *Staphylococcus* (CoNS) and *Streptococcus* pathogens compared with *Staphylococcus. aureus* (*S. aureus*) within various European registries (United Kingdom (UK) and Sweden) [2,3].

Peel *et al.* [4] showed that causative pathogens in PJI differ significantly in Australia compared to other reported studies and geographic regions such as the US, Sweden and the UK. In particular, the rates of polymicrobial infections showed high differences (36 vs. 14 %), as did the isolation of MRSA (over 40 % of all cases), as compared to previous European and US reports.

Pakroo *et al.* [5] reported similar geographic variation in organisms causing spinal infections in patients presenting to a tertiary referral center in the UK. The epidemiology and antibiotic susceptibility of bacteria causing skin and soft tissue infections do show geographic variation (e.g., between US, Germany, Italy and Spain) differentiating between MRSA, methicillin-sensitive *Staphylococcus aureus* (MSSA) and CoNS pathogens [6]. Although these data which relate predominantly to general skin infections cannot be easily transferred to PJI, it has been well accepted that such local infections (at the time of surgery or after) subsequently might lead to PJI.

Furthermore, it has been shown that community-acquired soft tissue MRSA infections have a much higher incidence in the US compared to Europe [7]. While a large percentage of soft-tissue infections are caused by community-acquired MRSA in the US, the community-acquired MRSA cutaneous infection rate in Europe only accounts for between 1 and 3% of presenting wound infections [8].

Along with this geographic variability, Anthony *et al.* [9] found a seasonal variability of surgical site infection (SSI) in total knee arthroplasty (TKA) and total hip arthroplasty (THA), with seasonal increase of SSI between 30 and 19% in patients with TKA or THA procedures respectively in the summer months, suggesting the possibility that geographic temperature conditions might influence the incidence and etiology of PJI. This data was extracted from a US National Database.

Data from several multicenter, retrospective studies has demonstrated that the organisms causing PJI vary by country or region of the world. An increasing number of PJIs are being caused by more virulent and resistant organisms such as MRSA in the US and Australia. With the literature lacking large prospective studies, we assign a moderate recommendation.

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Fungal Periprosthetic joint infection

4.1. FUNGAL PERIPROSTHETIC JOINT INFECTION: DIAGNOSIS AND TREATMENT

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QUESTION 1: What is the optimal method to diagnose fungal periprosthetic joint infection (PJI)?

RECOMMENDATION: Diagnosis of fungal PJIs is established by incubating joint aspirations or tissue samples collected intraoperatively on specialized culture media. Furthermore, isolation of fungal species may take up to four weeks. However, given the shortcomings associated with the use of culture, alternative techniques capable of detecting fungi, such as molecular techniques, may be used as an adjunct.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

PJIs can be caused by an expanding number of infecting organisms. While the vast majority of these organisms are gram-positive cocci, atypical organisms such as fungi have also been shown to be associated with PJIs and present an even more difficult diagnostic challenge [1,2]. In the largest series published, 31 fungal PJIs presented with indolent onset of joint swelling and pain frequently without other systemic symptom or signs of infection [3]. In another series, about 50% of patients who had fungal PJIs had radiographic evidence of loosening [4] and could be misdiagnosed as aseptic loosening, especially for those having normal serum inflammatory markers [5]. Serum C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) joint fluid cell counts and bone scintigraphy have limited value for diagnosis of fungal PJIs [6–8]. While the aforementioned tests all help to establish the presence or absence of an infection, they provide no information regarding the identity of the infecting organism.

Perioperative cultures, such as aspirated synovial fluid, as well as intraoperative tissue and swab samples, have been considered diagnostic standards for fungal PJIs [3,4,10,11]. Unfortunately, culture has been shown to have sensitivity as low as 50%. Given that these studies were assessments of the overall accuracy of culture in diagnosing PJI and not fungal infections specifically, culture may even perform worse in the setting of fungal PJIs [12–16]. Fungi are notoriously difficult to isolate in culture due to several reasons. First, culturing fungi requires the use of specialized media, with various modifications needed in order to isolate different species of fungi [17]. The universal media for most fungi is Sabouraud dextrose brain heart infusion (BHI) agar or plain BHI agar [18]. A blood-containing media such as BHI agar with 10% sheep blood improves the sensitivity or recovery of dimorphic fungi. Special media are required for fastidious organisms, such as bird seed agar for *Cryptococcus neoformans*, chromogenic agar for Candida, dermatophytes' test medium for dermatophytes, and longchain fatty acid supplementation for *Malassezia furfur* [19]. Second, the traditional duration to culture slowly growing fungi requires four weeks or longer. A study of 3,036 fungal cultures showed that an incubation period of two weeks is sufficient for the detection of yeast or molds, whereas, a four-week incubation period is necessary for dermatophytes [18]. Given the potential for identifying a fungal organism up to a month following resection arthroplasty, more expeditious methods of pathogen identification are needed. The vast majority of techniques have focused on sequencing of the 16S segment, a highly conserved region of bacterial DNA that allows for identification of bacteria at the species level [15,20,21]. Thus, many of these techniques are unable to identify fungal organisms; however, sequencing of the Internal Transcribed Spacer segment, a fungal sequence analogous to the 16S segment [22,23], demonstrated a sensitivity of approximately 90%, with a turnaround time of a week, a massive improvement over culture [24].

In conclusion, culture remains the primary method for identification of fungal organisms in the diagnosis of PJIs. However, in light of the difficulties associated with isolation of fungal organisms, alternative techniques are needed. Techniques capable of detecting fungal organism, such as next generation sequencing (NGS), may be used as an adjunct in the diagnosis of fungal PJI.

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QUESTION 2: Should patients with periprosthetic joint infections (PJIs) caused by a fungus undergo the typical two-week antimicrobial holiday prior to reimplantation?

RECOMMENDATION: There is no conclusive evidence to support the use of an antimicrobial holiday period prior to reimplantation in case of fungal PJI treated with staged revision.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 90%, Disagree: 5%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

The review of the literature on fungal PJIs treated with staged revision shows only 8 retrospective cohort studies (level of evidence IV) and 13 case reports (level of evidence V) (Table 1). We have been able to find only 21 papers (104 patients) regarding fungal PJI treated with two-stage exchange arthroplasty. In 68 cases (from 14 different studies), a drug holiday of at least two weeks was applied before reimplantation. No drug holiday was prescribed in two cases. For the remaining 34 patients, there was no data available about this aspect. Candida spp. (especially *albicans* or *parapsilosis*) was the main causal agent. Most patients had at least six weeks of systemic antifungal treatment after first operation, in agreement with the 2013 Consensus Conference conclusions. Following reimplantation, antifungal agents were continued for from two weeks to six months in six studies (69 patients). The agent most frequently used was fluconazole. Among reviewed papers, most authors seem to prefer a drug holiday of two or more weeks before second surgical stage. This approach is consistent with the conclusion of the previous Consensus Conference in 2013. No study compares the results of the two different strategies.

In conclusion, antifungal therapy could be stopped before reimplantation but there is no high-quality evidence to support this opinion.

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TABLE 1. Retrospective cohort studies regarding the recommendation duration of systemic antifungal agents for fungal periprosthetic joint infection treated with two-stage exchange arthroplasty

Author	Year	N	Organism	Length of Anti-fungal Therapy	Length of Interstage	Drug Holiday	Outcome
Hennessy [1]	1996	1	*C. parapsilosis*	13 w	not known	not known	cured
Ramamohan [2]	2000	1	*C. glabrata*	6 w	6 w	0	cured
Yang [3]	2001	1	*C. parapsilosis*	10 w	3 m	2 w	cured
Baumann [4]	2001	1	*A. fumigatus*	6 w	8 w	2 w	cured
Phelan [5]	2002	10	Candida spp.	25 w (2-49)	6.7 m (8 days-17.7 m)	1.4 m	8 cured
Cutrona [6]	2002	1	*R. minuta*	not known	12m	not known	cured
Wyman [7]	2002	1	*C. tropicalis*	not known	not known	not known	cured
Azzam [8]	2009	31 (19 with two-stage)	*C. albicans* (20) *C. parapsilosis* (4) both above (3) *C. glabrata* (1) Aspergillus (1) Others (2)	6 w after RA 6 m after reimplantation	7 m (range 2-14)	≥2 w	9 cured/ 10 failed
Dutronc [9]	2010	7 (3 with two-stage)	*C. albicans* (4) *C. parapsilosis* (2) *C. guilliermondii* (1)	not known	not known	not known	1 cured/ 2 failed
Wu and Hsu [10]	2011	1	*C. albicans*	17 w after RA 6 m after reimplantation	6 m	7 w	cure
Yilmaz	2011	1	*A. fumigatus*	6 w	4 m	10 w	cure
Graw [11]	2010	2	*C. albicans*	12 w	not known	8 w- 1 y	failed
Hwang [12]	2012	28	*C. parapsilosis/albicans*	≥6 w after RA A maximum of 6 m after reimplantation	9.5 w (6-24)	not known	22 cured/ 4 failed
Anagnastakos [13]	2012	5	*C. albicans (2)* *C. lypolitica* *C. albicans+C. glabrata* *C. glabrata*	6 w	12.8 w (12-14)	6.8 w (6-8)	cured
Kuiper [14]	2013	8 (4 with two-stage)	*C. albicans* (6) *C. albicans* + *C. glabrata* *C. parapsilosis* (1)	8.75 w (1w-5mo)	6.5 m (4-14 m)	>8 w (8-50w)	2 cured/ 2 failed
Deelstra [15]	2013	1	*C.albicans*	not known	not known	no	cured
Ueng [16]	2013	8	Candida spp	14 m after RA (3-18 m) 2.5 m after reimplantaiton	not known	≥2 w	8 cured/ 1 deceased

Author	Year	N	Organism	Length of Anti-fungal Therapy	Length of Interstage	Drug Holiday	Outcome
Reddy [17]	2013	1	*C. tropicalis*	18	20 w	2 w	cured
Wang [18]	2015	5	Candida spp	8 w after RA (6-10) 2 w after reimplantation	6 m	>2 m	5 cured
Geng [19]	2016	8	*C. albicans* (3) Mould *C. freyschussii* Aspergillus spp *C. parapsilosis* *C. glabrata*	2.8 m after RA (1.5-6) 1m after reimplantation (1m-46 days)	4.3 m (3-7)	6 w (2w-10w)	7 cured
Sebastian [20]	2017	1	*C. tropicalis*	24 w	9 m	3 m	cure

RA, resection arthroplasty

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QUESTION 3: Can debridement, antibiotics and implant retention (DAIR) be used to treat acute fungal periprosthetic joint infections (PJIs)?

RECOMMENDATION: DAIR has a relatively high failure rate in fungal PJIs, especially for immunocompromised patients. DAIR should be reserved for patients with truly acute PJIs after an index arthroplasty and in healthy patients (Type A). If DAIR is performed for fungal PJIs, consideration should be given to anti-fungal suppression therapy.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 91%, Disagree: 5%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

PJIs caused by fungal pathogens are a rare occurrence accounting for <1% of all PJIs [1]. Surgical treatments for fungal PJIs include DAIR, one-stage exchange arthroplasty and two-stage exchange arthroplasty. The difficultly in the treatment of fungal PJIs can be attributed to the rarity of fungal PJIs that have confined our understanding of this infectious entity and the often-immunocompromised status of patients who develop these infections in the first place. Although some general agreements have been reached with recommendations proposed by the International Consensus Meeting (ICM) and Infectious Diseases Society of America (IDSA) [2,3], many issues related to fungal PJIs remain unresolved. The most optimal surgical option for patients with fungal PJIs, the dose and the type of antifungals to be added to the polymethyl methacrylate (PMMA) spacer, the optimal duration of systemic antifungal treatment and many other issues still remain unanswered.

In addition, despite offering a potential explanation above, the exact reason for the less optimal outcomes of treatment of fungal PJIs remains unknown. It is, however, known that patients with

fungal PJIs often have an immunocompromised condition, such as diabetes mellitus, rheumatoid arthritis and cancer, which may markedly contribute to the high failure rate of treatments [3]. In addition, the complexity of the fungal biofilm in having a highly heterogeneous structure in response to environmental conditions, such as differences in pH, oxygen availability and redox potential, could also contribute to the suboptimal outcomes of treatment [4].

Overall, DAIR has been reported to have a relatively high failure rate in patients with PJIs caused by resistant organisms and poor hosts. DAIR as a surgical option for patients with fungal PJIs is questionable [5], and a study published in the *New England Journal of Medicine* listed fungal PJIs as a contraindication for DAIR [6]. A search of Medline, PubMed, Embase, Web of Science and Medscape revealed no reports in the setting of DAIR for acute fungal PJIs. The review of the English literature from 1979 to 2018 identified 22 fungal PJIs undergoing DAIR [7–19]. An overall high failure rate (82%, 18 of 22) was reported for these patients. Additionally, one study by Azzam et al. demonstrated a 100% failure rate for seven patients in their cohort undergoing DAIR [16]. Among the seven patients who failed, five needed resection arthroplasty and two needed chronic suppression with oral fluconazole [16]. Furthermore, Badrul et al. reported a fungal PJI case treated with debridement and oral fluconazole for a year. But, the infection was never totally cured and a secondary infection with methicillin-resistant *Staphylococcus aureus* (MRSA) developed [14]. Fabry et al. also reported a failure in a patient who underwent two debridements and an eight-month oral antifungal therapy regimen [15]. However, a few case reports demonstrated successful results at a minimum follow-up of two years and all of them required a six-months to one-year antifungal agent treatment after irrigation and debridement alone [9,11,12,18,19].

Given the fact that literature is not definitive on this issue and based on the available reports, we recommend that DAIR for fungal PJIs should be limited to those with early presentation, good soft tissue coverage, well-fixed implants and are healthy patients (Host type A). If DAIR is performed for patients with fungal PJIs, long-term suppression (six months or longer) with antifungal agents should also be considered.

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QUESTION 4: Which antifungals, route of administration and duration of treatment should be utilized to treat fungal periprosthetic joint infections (PJIs)?

RECOMMENDATION: Fluconazole, by both oral and intravenous routes, is currently the treatment of choice for PJIs due to susceptible fungi, including the *Candida* species which are responsible for the majority of fungal PJI cases. Amphotericin B lipid formulations or echinocandins given intravenously are secondary considerations, but may be less well tolerated. Culture data including antifungal susceptibilities should be used to guide therapy. Two-stage revision is currently the standard of care. Antifungal treatment should be administered during the spacer interval with a minimum treatment duration of six weeks. Following revision, treatment with oral fluconazole (400mg daily) should be continued for three to six months, if tolerated.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Fungal PJIs are uncommon, accounting for approximately 1% of PJIs [1,2]. *Candida* species, in particular *Candida albicans*, are by far the most common pathogen [1,3]. Concomitant bacterial infection may occur in up to 20% of cases [4]. Risk factors for fungal

PJIs include immunosuppression, systemic disease and extended antimicrobial therapy [5]. *Candida* infections are associated with biofilm formation which plays a key role in the development of PJIs [5,6]. Given the infrequency of fungal PJIs, there are no standard guidelines regarding treatment. The current literature contains retrospective case series and case reports. There are no randomized clinical trials, prospective cohort studies or case-control studies to guide therapeutic decisions.

Candida PJI has been treated successfully with antifungal therapy alone in several case reports [7,8]. Two-stage revision, however, is regarded to be the current standard of care for the surgical management of fungal PJI as high failure rates have been reported with primary debridement. Debridement, antibiotics and implant retention (DAIR), as well as single-stage revision, were shown to have a failure rate of up to 50% [1,2,9,10]. A two-stage revision with interval antibiotic therapy is consistent with the Infectious Diseases Society of America (IDSA) guidelines for bacterial PJI [11]. The role of antifungal eluting bone cement is controversial. Fluconazole is not currently available as a sterile powder. Both amphotericin B and voriconazole can be added to cement. Data show that voriconazole is more effectively released than amphotericin B and that it achieves and maintains high intra-articular concentrations [12–17].

Systemic antifungal therapy is administered during the spacer interval. Treatment options include fluconazole (400mg (6mg/kg) PO/IV daily), an echinocandin (caspofungin 50 to 70mg IV daily, micafungin 100mg IV daily or anidulafungin 100mg IV daily) or lipid formulation amphotericin B (3-5 mg/kg IV daily) [18]. The minimum duration of antifungal therapy after resection should be 6 weeks with up to 12 weeks considered. Revision surgery should be delayed three to six months in most cases [18,19]. Antifungal therapy should be discontinued and aspiration of the joint space should be culture-negative prior to revision. Following revision, fluconazole (200mg to 400mg PO daily) should be continued for a minimum of six weeks with up to six months or longer considered [2,5,18,20].

The incidence of fungal PJI is expected to rise given the increasing number of joint arthroplasties performed each year [21]. While specific guidelines for the management of fungal PJI have yet to be established, important considerations in management include confirmation of microbiologic diagnosis including antifungal susceptibility testing of fungal isolates, surgical options with two-stage exchange arthroplasty currently favored, the use of antifungal eluting cement and long-term systemic antifungal therapy.

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Treatment

5.1. TREATMENT: ALGORITHM

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QUESTION 1: Should early postoperative infection and acute hematogenous infection be treated and managed differently?

RECOMMENDATION: There is no evidence to support the notion that early postoperative infection and acute hematogenous infection should be treated differently as long as the onset of symptoms is <4 weeks (favorable <7 days), implants are well-fixed, no sinus tract exists and the isolated infecting organism is sensitive to an antimicrobial agent.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 94%, Disagree: 5%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Early postoperative infection is usually defined as infection occurring within three weeks of index arthroplasty, although some authorities state that any infection within three months (90 days) of the index arthroplasty should be considered acute [1]. Hematogenous infections associated with a remote source are often classified as late infections, which can occur one to two years after arthroplasty [2]. Acute hematogenous infection is defined as infections with no more than three weeks of symptoms [3]. According to the Clinical Practice Guidelines by the Infectious Diseases Society of America (IDSA), patients who have a well-fixed, functioning prosthesis without a sinus tract, infection occurring within 30 days of index arthroplasty or <3 weeks of onset of infectious symptoms and having an organism susceptible to oral antimicrobial agents, should be candidates for debridement antibiotcs and implant retention (DAIR) [4]. The International Consensus Meeting (ICM) 2013 also proposed that DAIR should be considered in patients with infection occurring within three months of the index arthroplasty, with less than three weeks of symptoms in early postoperative infections and those with symptoms less than three weeks in late hematogenous infection [3]. When these criteria are met, DAIR is a reasonable option for early postoperative or acute hematogenous infection. However, because of the relatively high failure rate of DAIR in some reports and the fact that mature biofilm on an implant surface forms within a few days, some studies have suggested that DAIR should be restricted to patients with less than five days of infection symptoms [5].

One prospective study demonstrated that 52% of acute hematogenous infections failed at two-year follow-up following DAIR [6]. Treatment failure rates were 57.8% in staphylococcal infection, 14.3% in streptococcal infections and no failures were seen in gram-negative PJI [6]. A second comparative study reported that the success rates after DAIR in hip and knee PJI may be significantly increased if treatment was initiated within two days of symptoms [7]. In the latter study, DAIR showed overall success rate of 82.1% for early infections and 57.1% for acute hematogenous infections. Patients with acute hematogenous infections had an eight-fold higher chance of failure. Given the higher failure rate in the acute hematogenous group, the authors suggested that treatment parameters for these infections required additional studies with higher patient numbers [7]. A recent study evaluating the outcome of DAIR showed no statistically significantly different treatment outcome between early postoperative infection (15%) versus acute hematogenous infection (21%) [8]. Modular components were exchanged in only 70% of the included patients in the latter study. Systemic host grade A (McPherson classification) was a strong predictor of treatment success [8].

Several systematic reviews suggest that interventions in both early postoperative and acute hematogenous infections should be timely and aggressive (with exchange of modular parts), as each additional day of waiting lowers the odds for a successful outcome [9–12]. A recent meta-analysis reported the significant determinants of successful outcome following DAIR [12]. Time from onset of symptoms or index arthroplasty (< 7 days) and the exchange of modular components were the most significant factors influencing outcome. In the latter meta-analysis, the authors detected that the reported success of DAIR has increased since 2004 [12]. The exact reason for this improvement in outcome is not known but may relate to a publication in 2004 by Zimmerli et al. which established an algorithm for DAIR [10]. The algorithm may have encouraged the orthopaedic community to change their indications for DAIR, attempt to optimize patients prior to DAIR by modifying risk factors for failure and possibly altering the administration of antimicrobial regimen.

Virulent organisms causing PJI are also predictors for treatment failure following DAIR, according to some studies. *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA) have been reported to result in a higher failure rate following DAIR when compared to gram-negative pathogens [9,13]. In addition, infections with methicillin-resistant *Staphylococcus epidermidis* (MRSE) and vancomycin-resistant enterococci (VRE) have been associated with inferior outcome following DAIR [9,10]. In contrast, in a study on early postoperative and acute hematogenous infections caused by *S. aureus*, this difference could not be shown [14].

Acute hematogenous infection might be a marker of poor general health as almost half of the patients in one study had some critical medical comorbidity that may have predisposed them to developing infection in the first instance [15]. Relative high mortality rates around 20% after 2 years has been reported for patients with acute hematogenous infections, which could be attributed to higher rates of systemic sepsis at presentation in this patient population [14,15].

In conclusion, DAIR is a viable option and a reasonable first therapeutic approach for patients with early postoperative and acute hematogenous infections. However, some studies have reported a high failure rate of this surgical treatment and a relatively high early mortality rates after DAIR for acute hematogenous infections compared to acute postoperative infections. These differences might be related to differences in the pathoetiology of these infections and the influence of the intrinsic host factors on the outcome. Therefore, studies focusing on improving treatment outcomes after acute hematogenous infections are desperately needed.

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QUESTION 2: Should operative treatment differ in patients with systemic sepsis in the setting of periprosthetic joint infection (PJI)?

RECOMMENDATION: Yes. Patients with systemic sepsis in the setting of PJI should have surgical bioburden reduction, either with implant retention or resection of components (if indicated and safe), along with concurrent anti-microbial therapy. Reimplantation should be delayed until sepsis is resolved.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 79%, Disagree: 19%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Infection of total joint arthroplasty is a known and devastating complication all surgeons seek to avoid. Despite best efforts, prosthetic joints can be seeded from local and systemic sources [1–9]. Although PJI usually presents without systemic signs of pyrexia, chills and other symptoms, occasional PJI may result in systemic sepsis when the blood culture may also be positive for infection. In the context of systemic sepsis, hematogenous spread is the definitive mechanism by which PJI develops in previously well patients. Orthopaedic infections appear to be caused by the same common group of bacterial pathogens. In this group, the majority are gram-positive cocci, namely, *Staphylococcus aureus* and *Staphylococcus epidermidis*. There is the ever-present threat of methicillin-resistant *Staphylococcus aureus* (MRSA) as a difficult PJI infection to remove. Moreover, the growing number of vancomycin-resistant enterococcus and other serious gram-negative bacteria are also a concern. Gram-negative bacteria are associated with more severe episodes of sepsis due to the production and release of lipopolysaccharides (endotoxin).

Highlighted across several studies is the concept of the arthroplasty surface acting as a unique microbial substratum [10]. Gallo et al. reported the affinity of *S. epidermidis* to attach to polyethylene surfaces as opposed to *S. aureus* preference for bare metal. In each of the papers examined by Gallo et al. the presence of biofilm on the wearing or corroded surfaces of the implants was a key factor in the bacterial resistance to host and antimicrobial attack. A paper referenced in the Gallo et al. review by Gristina [11], characterised the colonization of the prosthesis as a "race for the surface" [10]. This concept is apt at highlighting the need for pathogens to colonize, undeterred by local and host factors.

These concepts are of pivotal importance when examining the published material reviewed here in the context of the original question, "to evaluate whether operative treatment should differ in patients with systemic sepsis in the setting of prosthetic joint infection." As demonstrated in this review and supported by the significant cohort size, PJI can occur as a consequence of local or hematogenous colonization. Overall, severity of infection is higher with hematogenous spread [12–14], as is the difficulty in clearing the infection for subsequent implant revision. Osteomyelitis prior to implantation of prosthetic joints indicates increased risk as

reported by Jerry et al. [4]. The nearly 5-fold increase in recurrence rates seen in patients with prior bone infection serves as a significant warning to surgeons to adequately debride as much contaminated surface as is feasible to allow for control of infection and subsequent implantation.

Based on the articles included in this review, there is no evidence to suggest that the implantation of prosthetic joints during an episode of sepsis is advisable. Often, however, joint arthroplasty procedures will need to be performed to alleviate the tremendous pain associated with infective destruction of a joint surface. Each of the included studies recommended a staged approach to surgical management of PJI with the most common approach being two-staged revision. There is very limited evidence to support retention of implants if a curative outcome is the main objective of the treatment. Also, there is a lack of evidence to suggest initiating antibiotic therapy to counter the systemic sepsis before the first-stage revision surgery. Though, identification and eradication of clinically obvious secondary foci, like indwelling catheters and skin, soft tissue, respiratory and genito-urinary infections, could be of vital importance for controlling the PJIs and preventing subsequent relapse. Therefore, like PJIs without systemic sepsis, a combination of effective debridement and concurrent intravenous antimicrobial therapy is the current best practice standard of care. The main limitation associated with the effective execution of this thorough and proven care strategy seems to be the accurate diagnosis of the complete clearance of infection to restore *aseptic* status to the patient.

It must be noted, as of the completion of this review, there are no studies that directly evaluate whether operative treatment should differ in patients with systemic sepsis in the setting of PJI. There are a number of closely related papers quoted above, but that is the limit of current knowledge. It is, however, our opinion that patients with systemic sepsis exhibiting constitutional symptoms are at serious risk and should be treated urgently. The best option of treatment is bioburden reduction which involves extensive soft tissue debridement and removal of infected prostheses.

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QUESTION 3: What should be done for patients with persistent wound drainage (PWD) after total joint arthroplasty? What are the indications for surgical intervention?

RECOMMENDATION: Management of draining wounds after total hip arthroplasty (THA) or total knee arthroplasty (TKA) consists of two main steps; nonoperative and operative. The nonoperative measures include: modification of venous thromboembolism (VTE) prophylaxis, nutritional supplementation, dressing measures (such as negative pressure wound therapy (NPWT)) and restriction of range of motion. If draining continues for more than seven days after implementing the nonoperative measures, operative interventions may be indicated – including irrigation and debridement, synovectomy and single-stage exchange. In certain situations, superficial wound washout may be indicated (Fig. 1).

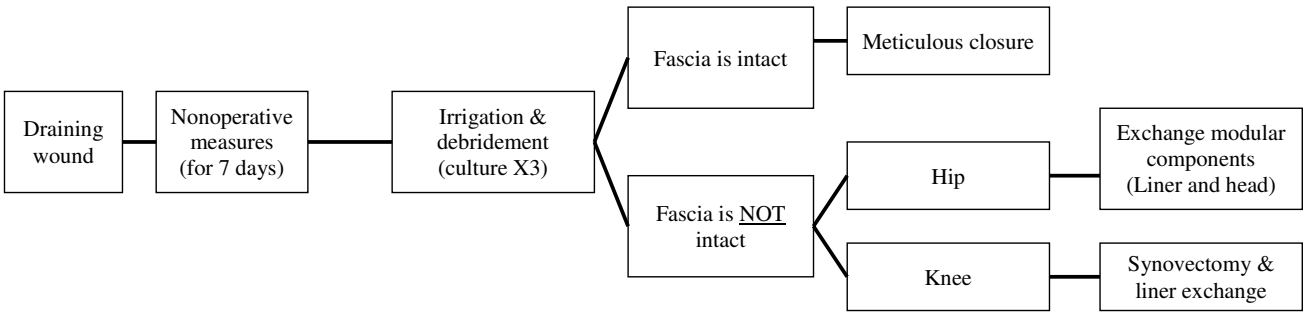

Figure 1. Management of draining wounds after total joint arthroplasty.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Drainage after THA and TKA increases the risk of subsequent superficial or deep infection. Studies have shown that the risk of deep infection increases by 29% after TKA and 42% after THA with each additional day of drainage [1].

Definition

Persistent wound drainage (PWD) by definition is an area of drainage greater than 2 x 2cm on the incisional gauze that persists over 72 hours postoperatively [2]. Drainage can be due to hematoma, seroma, fat necrosis or defects in arthrotomy closure [3].

Nonoperative Measures

Ceasing anticoagulation agents: Anticoagulation agents for VTE prophylaxis have been shown to affect PWD after THA and TKA. Low molecular weight heparin (LMWH) leads to higher rates of prolonged wound drainage after THA and TKA compared to aspirin and warfarin [1]. Fondaparinux had fewer wound complications but no difference in infection after TKA compared to aspirin, LMWH or warfarin [4]. Dabigatran was found to have an increased rate of wound drainage and increased length of stay following TKA and THA [5]. Therefore, one of the first steps in patients with PWD is to cease the anticoagulation medications, if possible.

Negative pressure wound therapy: NPWT applied to closed incisions following TKA or THA has been shown to reduce the rate of superficial wound infection [6]. In patients undergoing primary total hip or knee arthroplasty, NPWT has been shown to reduce post-surgical wound exudate, number of dressing changes, a trend toward reduced length of stay and a trend toward reduced post-op surgical wound complications [7]. Using ultrasound to measure volume, NPWT has been shown to reduce the size of post-op seromas when compared to a standard dressing [8]. NPWT applied 3-4 days after THA for persistent drainage resulted in drainage resolution in 76% while 24% required further surgery [9]. As part of local wound care in the first 7 days of PWD, we recommend using incisional NPWT systems.

Nutrition: Malnourishment has several definitions. One of the most commonly used ones is: serum transferrin <200mg/dL, serum albumin <3.5g/dL or total lymphocyte count <1500/mm3. Poor nutritional status is associated with a significant (up to 5-fold) increase in risk of wound complications following THA and TKA [10–12]. Malnourished patients are more likely to fail nonoperative treatment (odds ratio (OR) 18.29), as well as surgical debridement (35% vs. 5%, p<0.0003) [3]. We strongly urge modifying the nutritional status of the patients prior to an elective arthroplasty procedure. In case of a PWD, postoperative nutritional supplements can help to improve the wound healing process.

Surgical Intervention

Surgical intervention for drainage should be considered after five to seven days of PWD [1–3]. Saleh et al. [2] conducted a 20-year surveillance study and concluded that patients with longer than five days of drainage have 12.7 times higher likelihood to develop surgical site infection in comparison with those who had less drainage time. Therefore, we recommend proceeding with surgical intervention if the PWD continues for more than seven days.

The first step of the surgical intervention is irrigation and debridement (I&D) and obtaining at least three intraoperative cultures. Irrigation is recommended to be performed with at least 9 liters of an irrigation solution, such as normal saline or an aqueous iodophor solution. At this point if the fascia is found to be intact, we recommend meticulous closure. However, if the fascia is not intact, modular components should be exchanged [1,3]. Studies have shown promising results with single I&D. Jaberi et al. [3] reported that in THA and TKA patients with PWD, drainage stopped in 76% of patients after single-stage I&D. The remaining 24% required subsequent treatments such as repeat I&D, removal of implant or long-term antibiotic administration.

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QUESTION 4: How should infected bilateral hip or knee arthroplasties be managed?

RECOMMENDATION: The optimal surgical treatment for infected bilateral hip or knee arthroplasties is unknown. While revising the components likely provides improved outcomes over limited debridement with component retention, data does not preferentially support either a single-stage or two-stage exchange revision arthroplasty

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 83%, Disagree: 11%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Infected bilateral hip or knee arthroplasties present a rare treatment dilemma for both the patient and surgeon. The literature on this topic is limited, however, with only two small case series and at least nine case reports describing multiple simultaneous periprosthetic joint infections (PJIs) [1–17]. Treatment options include debridement with component retention, single-stage revision and two-stage revision surgery. The largest study by Wolff et al. on infected bilateral total knee arthroplasty demonstrated improved outcomes with a simultaneous two-staged revision when compared with irrigation, debridement and prosthetic salvage [6]. Concerns exist about the morbidity of a two-stage revision and the immobility and restricted weight bearing on both extremities during the antibiotic spacer period. A series of 16 bilateral infected arthroplasty patients by Zeller et al. noted good results with single-stage exchange and another center reported two cases of successful treatment of bilateral infected THA with a simultaneous single-stage revision [7,17].

Surgical treatment of bilateral infected arthroplasties should consider factors such as the virulence of the organism, medical comorbidities, patient age and functional status. For bilateral acute hematogenous infection, some authors performed an irrigation, debridement and exchange of modular bearing surfaces followed by targeted antibiotic therapy, but these results were limited to case reports [5,8–13,15,16]. For chronic bilateral periprosthetic infections, these case reports described the same therapeutic management as is commonly favored for unilateral infection: two-stage revision with placement of an antibiotic impregnated cement spacer for a period of at least 6-8 weeks before reimplantation [9,14,15]. An interval of several days occurred between each side undergoing surgery in these series, while others performed simultaneous bilateral revision surgery. The decision whether to perform simultaneous bilateral revision surgery for PJI should also consider the patient's medical comorbidities and functional status. With only small retrospective case series in the literature, we can issue a limited recommendation that revising the components likely results in improved outcomes, however we do not have the data to recommend a single-stage or two-stage revision procedure over the other.

We do, however, feel that performing resection arthroplasty of two joints under the same anesthesia represents immense physiological insult to the patient and all efforts should be made to minimize the operative time and blood loss in these patients if bilateral surgery is contemplated. The use of two expert teams to operate at the same time has been suggested by some investigators.

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5.2. TREATMENT: DEBRIDEMENT AND RETENTION OF IMPLANT

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QUESTION 1: What are the indications and contraindications of using debridement, antibiotics and implant retention (DAIR) with exchange of modular components for the management of periprosthetic joint infection (PJI)?

RECOMMENDATION: The best advantage in performing DAIR of the prosthesis is seen in early postoperative PJI and acute hematogenous PJI, defined as symptoms existing for no longer than four weeks, and if the implant is stable. The KLIC and CRIME80 scores may aid in risk stratification.

LEVEL OF EVIDENCE: Moderate

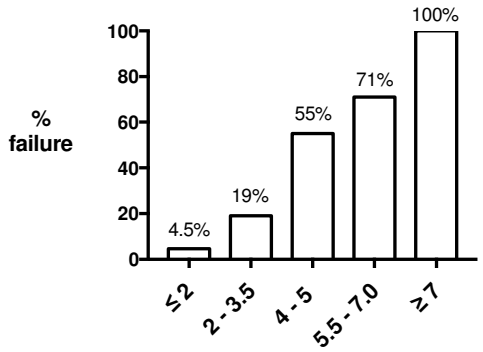
DELEGATE VOTE: Agree: 80%, Disagree: 18%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Open DAIR of the prosthesis is considered a less disruptive intervention that seeks to preserve a functional implant and forego the significant morbidity of implant removal and subsequent surgical procedures. While DAIR remains a viable and a less morbid alternative to resection arthroplasty, recent studies have demonstrated that an unsuccessful procedure is strongly associated with failure of future two-stage revision [1].

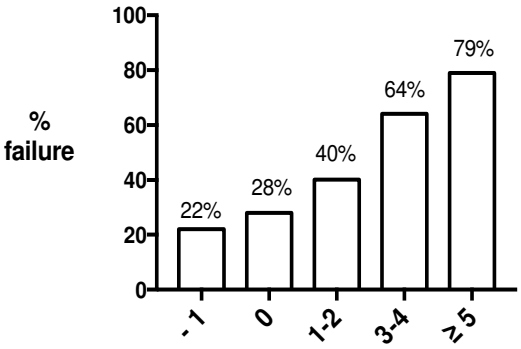
Strictly speaking, there are no absolute contraindications to perform a DAIR procedure, but a DAIR should be discouraged when the chance of failure without removing the implant is very high. Therefore, chronic PJIs should be considered an absolute contraindication to perform a DAIR procedure, as a fully developed mature biofilm with the presence of "persister cells" excludes the possibility for cure without removal of the implant [2,3]. Indeed, Barberan et al. demonstrated in 60 elderly patients with a Staphylococcal infection, that when the duration of symptoms exceeds one month, the failure rate increases exponentially when a conservative treatment is chosen without removal of the implant [4]. Although the efficacy of DAIR in chronic infections have been reported to be around 50% in a recent systematic review with a limited number of 29 patients, the average follow-up of these patients was only one year [5]. Extending the duration of antibiotic treatment following debridement does not seem to increase the chance for cure. Byren et al. clearly demonstrated that prolonging antibiotic treatment for more than six months simply postpones, rather than prevents, failure [6]. For this reason, when the intention is to cure the PJI and the patient is medically fit for major surgery, chronic infections should undergo revision surgery with removal of hardware.

Failure rates following DAIR for acute PJI vary widely and range from 20 - 70%, with higher failure seen in acute hematogenous (late acute) PJI. Contraindications to performing a DAIR procedure in acute PJI are controversial. In general, all acute PJIs are candidates for debridement if the implant is well fixed, but several factors have been associated with an increased chance for failure. These factors include host and implant related factors, the severity and extensiveness of the infection, the duration of symptoms, the possibility to exchange the modular components during debridement and the causative microorganism [1,7–40]. In order to avoid surgery that has a very high risk of failure, selecting a subset of patients that are more likely to benefit from revision surgery instead of DAIR, would be helpful. A preoperative risk score has been developed to predict failure following DAIR for early acute Kidney, Liver, Index surgery, Cemented prosthesis and C-reactive protein value (KLIC-score, Fig. 1A) and acute hematogenous PJIs (CRIME80 score, Fig. 1B) [27,30]. These preoperative scoring systems could be used in clinical practice to select those patients who are most eligible for DAIR.



K	Chronic renal failure (Kidney)	**2**
L	Liver cirrhosis	**1.5**
I	Index surgery: indication prosthesis: fracture OR revision prothesis	**1.5**
C	Cemented prosthesis	**2**
	CRP > 115 mg/L	**2.5**

FIGURE 1A. KLIC preoperative risk score [27,30]



C	COPD	**2**
	CRP > 150 mg/L	**1**
R	Rheumatoid arthritis	**3**
I	Indication prosthesis: fracture	**3**
M	Male	**1**
E	Exchange of mobile components	**-1**
80	Age > 80 years	**2**

FIGURE 1B. CRIME80 preoperative risk score [27,30]

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QUESTION 2: Is debridement, antibiotics and implant retention (DAIR) an emergency procedure for patients with acute periprosthetic joint infection(PJI) or should patient optimization be implemented prior to surgery to enhance the success of this procedure?

RECOMMENDATION: DAIR is not an emergency procedure but should be performed on an urgent basis when the patient with acute PJI is medically and surgically optimized.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 97%, Disagree: 3%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

At the present time DAIR is reserved for patients with acute PJIs when no loosening of the implants is present [1,2]. Success rates vary among different studies from 16% - 82% [3–7]. The large majority of studies regarding DAIR focus on reporting the success rates or evaluating the factors that are correlated with success [2,4–6,8–16]. However, none of these studies have focused on the urgency of DAIR as a procedure.

DAIR should be considered an urgent, but not emergent procedure, as the time period from the onset of symptoms until the operation has been reported to be important factor affecting the success of the procedure [5]. Factors that are known to affect the outcome of DAIR include the type of infecting organism [5,10,17–21], duration of symptoms before intervention [4–7,11–13,17,20,21], type and duration of antibiotic therapy [6,14,22], age [11], erythrocyte sedimentation rate (ESR) values at presentation [4,13,19,20] , presence of underlying inflammatory conditions [4,19], exchange of modular components [7,17,23] and the presence of preoperative comorbidities like anemia [24].

An exact cutoff time beyond which DAIR should not be attempted has not been determined. Nevertheless, the duration of symptoms less than one week has been correlated to a higher success rate [4,5,7,12,17,21]. Furthermore, age of implant ≤ 15 days has been identified as a prognostic factor for successful DAIR [25].

There are patient-related factors and medical comorbidities, which, if not controlled, may result in severe complications and failure of the procedure. Comorbidities, such as rheumatoid arthritis, are not possible to adjust prior to debridement. However, correction of malnutrition, coagulopathy, anemia, hyperglycemia and diabetes should be pursued. Subjecting a patient to irrigation and debridement (I&D) without addressing an underlying coagulopathy could result in the development of a subsequent hematoma and its adverse effects. Thus, it is critical that conditions such as coagulopathy, nutritional status, uncontrolled hyperglycemia (>200 mg/ml), severe anemia (hemoglobin <10 mg/dL) and other reversible conditions are addressed prior to subjecting a patient to DAIR.

In conclusion, we therefore recommend that patients with acute PJI are evaluated on an urgent basis and the surgery is performed when patient is optimized from medical and surgical perspective.

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QUESTION 3: Does identification of the pathogen prior to performing debridement, antibiotics and implant retention (DAIR) help guide the surgeon's decision making? If so, should you wait, in a clinically stable patient, until the pathogen has been identified?

RECOMMENDATION: The identification of the responsible microorganism before DAIR is desirable. However, it should not prevent timely surgical intervention if delay in surgery is believed to promote further establishment of biofilm formation and compromise the outcome of surgical intervention.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

In implant related infections, the need for use of targeted antibiotics with proven action against the infecting pathogen and penetration into the biofilm has been suggested [1]. For instance, experts would likely agree DAIR is appropriate when ciprofloxacin-susceptible *Escherichia coli* is the infecting organism but, would probably discourage DAIR if the infective organism is a *Candida* spp. Thus, from a general perspective, knowledge of the pathogen prior to surgical intervention is desired. However, the real debate is whether waiting to determine the infective organism would adversely affect the outcome of DAIR and the timely intervention. The answer to this question requires an understanding of the implications of delaying DAIR and the consequences of performing DAIR without knowledge of the infecting pathogen.

Regarding the issue of time, Infectious Diseases Society of America (IDSA) guidelines, in conjunction with other authors, recommend a maximum of 21 days of symptom duration before utilizing DAIR to treat periprosthetic joint infection (PJI) [1,2]. This time limit, which has not been identified in comparative studies, is the same as that used in the pivotal clinical trial by Zimmerli et al. on the use of rifampin: none of the patients included in that cohort underwent DAIR beyond 21 days [3]. However, it remains uncertain whether these patients could have benefited from therapy if they had been submitted to DAIR more than 21 days after the beginning of symptoms. To this end, many observational studies have tried to find a precise cut-off of symptom duration, but heterogeneous populations with poorly reproduced results have emerged. Brand et al. observed that as little as a two-day delay in performing DAIR would significantly increase the odds of failure in a cohort of patients with staphylococcal PJI, mainly managed with β-lactams [4]. Other studies have also observed a poor outcome among patients with longer duration of symptoms without identifying a reliable time limit [5–13].

Inability to establish an optimal time threshold for DAIR may be mainly due to two causes. First, a short interval of time for performing DAIR may be a surrogate marker of severity of illness, since patients with sepsis or bacteremia are usually operated on sooner than more stable cases. Ill patients have a higher likelihood of failure [12,14], causing a short duration of symptoms to be paradoxically associated with a worse prognosis.Second, the duration of symptoms may be difficult to establish, especially in post-surgical cases where the postoperative inflammatory signs and pain may overlap the symptoms of infection. In these post-surgical cases, the prosthesis age before DAIR (i.e., the time from prosthesis placement to debridement) may be a more reliable variable. Yet, there is controversy on the definition of an early post-surgical infection that could be managed by DAIR. While IDSA guidelines do not recommend DAIR for patients with PJI that started greater than one month from the index arthroplasty [2], other important studies and the First International Consensus extend this period to three months [1,15]. Two large studies including staphylococcal and streptococcal PJI managed with DAIR found no differences in recurrent infection with a prosthesis age of less than one month versus those that were one to three months old [12,13]. Overall, it seems reasonable to assume that the sooner the DAIR is performed, the better the outcome will be, but there is insufficient evidence to recommend a specific time-limit of symptoms duration beyond which DAIR should be discouraged.

Bearing these considerations in mind, the question falls back onto the influence of the type of infecting microorganism(s) and its antibiotic susceptibility profile on prognosis. Apart from particular and rare situations such as the fungal infection previously mentioned or other multi-drug resistant bacteria, there is limited consensus on the impact of organism type on the outcomes of DAIR. Wide ranges of clinical success rates have been reported for common pathogens when managed by DAIR: 13% - 90% for *Staphylococcus aureus* [4,6,14,16–18], 27% - 94% for gram-negative bacilli (GNB) [8,14,17] and 40% - 94% for streptococci [19–24]. The largest observational studies performed to date set these cure rates in 55% for *S. aureus* [12], 58% for streptococci [13], 51% for enterococci [25] and 68% for GNB (with significant differences between fluoroquinolone-susceptible and -resistant strains: 79% vs.40%. respectively) [26].

Whether a 50% risk of failure should discourage use of DAIR is a matter of controversy. In older patients, Fisman et al. suggested an annual relapse rate ≈ 30% after DAIR to be cost-effective when compared with a two-step exchange procedure [27]. The potential advantages of a successful DAIR (one surgery, bone-stock preservation and less economic costs) [28] should be balanced with the consequences of failure. In this regard, conflicting results have been reported on the consequences of a failed DAIR. Sherrel et al. observed a higher likelihood of relapse among patients undergoing a two-stage revision after a non-successful DAIR, as compared with patients submitted to an elective two-stage exchange procedure [29]. However, these results have been contested by two other observational studies [30,31]. Furthermore, functional outcome has been reported to be identical in patients undergoing two-stage after failed DAIR compared to patients undergoing direct two-stage exchange [30, 31].

In summation, the type of infecting pathogen can be valuable information in the treatment algorithm for patients and surgeons considering DAIR. However, a prompt surgery is also of utmost importance. Therefore, the efforts to identify the causative pathogen for PJI should not cause undue delay in timely surgical intervention. Often, the pathogens of concern are virulent in nature and usually identified soon after culture samples are processed and cultured.

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QUESTION 4: Does exchange of all modular components during debridement, antibiotic and implant retention (DAIR) reduce the rate of surgical site infection (SSI)/periprosthetic joint infection (PJI) recurrence?

RECOMMENDATION: Yes. Exchange of all the modular components during DAIR reduces the risk of PJI recurrence.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Prosthetic joint infections in the early stage are commonly treated with DAIR. If successful, the outcomes of PJI treated by DAIR show functional outcomes and patient reported outcomes equivalent to those of primary total joint replacements [1]. During this procedure, the removal of modular components allows for better visualization of the knee, especially in the posterior aspect, thereby facilitating proper debridement and potential bio-burden/bio-film elimination. However, it is difficult to judge the necessity of exchanging the modular components during DAIR surgery due to the lack of conclusive evidence.

Our literature review identified several studies that support the exchange of modular components to reduce the rate of PJI recurrence [1–7]. Amongst these, six are retrospective and one is a meta-analysis [7] involving 39 retrospective case-control and cohort studies. Notably, all the studies included in this meta-analysis were also retrospective, making its strength of evidence inherently limited. Furthermore, the success rates after modular exchange during DAIR shows a wide range of variation from 18-83% among different cohorts in various studies. Such wide variations in the impact of modular component exchange suggests that the outcome of DAIR may be associated with multiple factors such as patient selection, thoroughness of debridement, type and virulence of the microorganisms, choice and duration of antibiotic regimen and the definition of treatment failure rather than the exchange of modular components itself. However, a recent systematic review [7] of DAIR performed for total hip arthroplasty showed that the mean proportion of success rate in studies where modular components were exchanged was significantly higher (73.9%) than studies in which no components were exchanged (60.7%). A multicenter review article [5] of 349 patients with *Staphylococcus aureus* PJI of both hip and knee replacements reported that modular exchange reduced the risk of failure by 33%. In addition, PJI review articles [8,9] and Choi et al. [2] study suggest that in total knee arthroplasty, not exchanging the polyethylene was an independent predictor of failure of DAIR (100% failure versus 59% success with modular exchange). Moreover, a recent case-controlled study [3] has shown the ten year implant survival rate of 86% with modular component exchange in DAIR (as compared to 68% without modular exchange) along with a fourfold increase in eradication rate. In contrast, there are several other studies which suggest that modular component exchange is not related to higher success rate of DAIR [8,10–15].

Due to the lack of conclusive evidence in the form of well-designed prospective randomized trials and standardized protocols, only a moderate strength of recommendation is provided for exchanging the modular components during DAIR to reduce the PJI recurrence rate.

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QUESTION 5: What is the minimum necessary volume of irrigation solution to use in debridement, antibiotics and implant retention (DAIR) treatment of acute periprosthetic joint infection (PJI)?

RECOMMENDATION: We recommend that 6-9L of irrigation solution, including saline or antiseptic solution such as sterile dilute povidone-iodine, is used during DAIR treatment of acute PJI.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

To date, there are no reported clinical studies relating to the optimal volume of irrigation required during DAIR treatment of PJI. However, variable outcomes have been reported with different institutions employing individual protocols for volumes of irrigation.

Few studies provide limited secondary data with regards to the ideal volume of irrigation to be used during total joint arthroplasty (TJA) in general and treatment of an infected joint in particular. In one such study, the authors were able to determine that four liters of sterile saline pulse lavage were sufficient to remove bone and polymethyl methacrylate (PMMA) debris exceeding 1µm in size from the joint during TJA. The authors extrapolated from their results that bacteria might effectively be removed with the same amount of irrigation given the similarity in size to the particulates assessed [1]. This model did not consider the effect of the developing bacterial biofilm on infected arthroplasty implants. DAIR has traditionally been thought to reduce the bacterial load and be effective in the acute period given that bacteria theoretically had not yet formed a glycocalyx biofilm. In another study, the authors used an in vitro model to determine the efficacy of biofilm removal from arthroplasty implants using high-pressure pulsatile lavage. Three liters of normal saline were used over an area measuring 1cm^2 recreating a prosthesis covered in *Staphylococcus aureus* biofilm. The authors concluded that pulse lavage is not able to sufficiently debride pre-existing biofilm. The volume of irrigation solution required was not investigated as a primary endpoint and the authors caution against extrapolating the results to clinical scenarios as their in vitro model potentially overestimated the amount of biofilm debrided by three liters of sterile saline pulse lavage [2]. More important than the volume of irrigation, researchers have found that the presence of staphylococcal infection, an elevated American Society of Anesthesiologists (ASA) score, or purulence were more likely to determine failure.

A comprehensive systematic review of the literature relating to open DAIR treatment of acute postoperative and hematogenous periprosthetic hip and/or knee joint infections, with or without modular component exchange, was performed. Databases searched include: PubMed, Embase, Cochrane Review and Google Scholar. Initial query generated 664 articles. Review articles and book chapters were excluded, while all references from such sources were screened for inclusion (spanning from 1990-2017). We included all Level I-IV studies that specified a certain volume of irrigation used per procedure and recorded the type of solution(s) used, mode of lavage administration, use of additive(s) and number of irrigation and debridements (I&Ds) performed. We included cases whereby some of the modular components may have been exchanged, but excluded those with dedicated planned staged exchanges. A total of 14 studies met the aforementioned criteria (Table 1) [3–16].

Typically, around 6 to 9L of solution were used during a single DAIR treatment, with 12 of the 14 studies utilizing up to 9L or more of irrigation solution. The evidence base for the specific irrigation volume is poorly defined within all studies, and recommendations for specific volumes in both primary and review articles reference consensus data obtained from previously published guidelines or individual protocols. [17–22] Therefore, this systematic review represents the body of evidence of actual irrigation volumes reportedly used in the literature.

No studies currently exist directly linking the necessary volume of irrigation to use in DAIR in acute PJI. Based on several retrospective studies, we extrapolate that the use of 6-9L of irrigation solution may be required when treating acute PJI. Prospective studies evaluating the volume of irrigation used as a study endpoint are required to better elucidate the optimal volume of irrigation in DAIR treatment of PJI.

TABLE 1. DAIR studies

Reference (Author, Year)	Study Design	n (acutePJIs)	Irrigation Solution	Additives	Volume Per Procedure (L)	Modular Revision	Infections Controlled
Mont et al (1997)	Prospective	24	NS	None	10	Yes	83%
Azzam et al (2010)	Retrospective	104	NS	Antibiotics	9	Some	44%
Estes et al (2010)	Retrospective	20	Castile soap solution	None	6 to 9	Yes	90%
Koyonos et al (2011)	Retrospective	102	NS	Antibiotics	9	No	35%
Royo et al (2013)	Retrospective	34	NS	Betadine/Peroxide	9	Some	74%
Kim et al (2014)	Retrospective	20	NS	Betadine	6 to 9	Yes	100%
Moojen et al (2014)	Retrospective	68	NS	None	3 to 6	Yes	21%
Koh et al (2015)	Retrospective	52	NS	None	9	Some	71%
Sousa et al (2016)	Prospective	23	NS	Chlorhexidine	7	Yes	85%
Tornero et al (2016)	Retrospective	143	Sterile Water	None	6 to 9	No	88%
Bryan et al (2017)	Retrospective	90	NS	None	6 to 9	Some	87%
Di Benedetto et al (2017)	Retrospective	20	NS	Betadine	6 to 9	Yes	80%
Duque et al (2017)	Retrospective	67	NS	Betadine/Dakin's/Bacitracin	12	Yes	69%
Narayanan et al (2017)	Retrospective	55	N/A	None	9	Yes	60%

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QUESTION 6: Is there a role for direct intra-articular antibiotic infusion following irrigation and debridement (I&D) for periprosthetic joint infection (PJI)?

RECOMMENDATION: The concept of achieving a minimum biofilm eradication concentration (MBEC) of antibiotics at the site of the infection is compelling. Despite the presence of retrospective studies reporting favorable outcome, because of heterogeneity in terms of adjunctive antibiotics, absence of a control group and small cohort size, the routine administration of intra-articular antibiotics in treatment of PJI is not justified. Prospective, randomized controlled trials (RCTs) are needed to support the routine use of intra-articular antibiotics as a stand-alone or adjunct treatment of PJI.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

Current published evidence for intra-articular antibiotic infusion following irrigation and debridement for PJI is limited to small case series and retrospective cohort studies. The authors of all studies aimed to achieve higher concentrations of antibiotics at the site of the infection than is possible with systemic therapy. PJI is associated with the presence of biofilms and sessile bacteria that are encapsulated within a biofilm matrix are more difficult to eradicate than planktonic bacteria [1–7]. Biofilm is the single most important factor causing resistance of bacteria to antibiotics in the treatment of PJI. While modest antibiotic concentration can prevent biofilm formation, eliminating established biofilm is a different matter. Bacteria protected by biofilm requires concentrations that are orders of magnitude greater than the minimal inhibitory concentration for the planktonic forms of the same bacterium to eliminate resistant organisms that are protected by the glycocalyx.

A systematic review of the literature revealed that biofilm encapsulated bacteria requires MBEC of antibiotics that are several orders of magnitude (100-1000+) above the minimum inhibitory concentrations (MIC) sufficient to eradicate planktonic bacteria (Table 1). Currently, MBECs at the site of the joint infection are not achievable with traditional intravenous (IV) antibiotic therapy without systemic toxicity (Table 1). IV antibiotics generally do not achieve these levels of concentration in synovial fluid, but instead achieve levels around two to three times the MIC.

Even though extensive work has been done to develop adjuvant agents such as antibacterial peptides and chelating agents to reduce the resistance of biofilm bacteria to antibiotics, the only clinically viable method available now is to apply antibiotics directly to the affected joint where the implant resides to achieve concentrations high enough to approach MBEC. The use of antibiotic-impregnated polymethyl methacrylate spacers is the most common method used to deliver antibiotics directly into the joint as part of treatment of PJI. While intra-articular concentration of antibiotics is significantly higher when antibiotic-loaded spacers are used, the level is still an order of magnitude (perhaps thousands of times) lower than what is needed to eradicate the biofilm. Local delivery of antibiotics with antibiotic-laden bone cement does not apply a consistent dose for enough time, with most the elution occurring in the first 48-72 hours and by day 5, the concentrations are often sub-therapeutic [8]. Time is an important factor in management of biofilm and exposure to high concentrations for long periods enhances the ability to achieve MBEC.

Direct antibiotic infusion through an infusion pump can achieve extremely high local levels of antibiotics for a prolonged period.In addition, when the antibiotic is delivered through an external portal, it can be discontinued if toxicity or sensitivity occurs. Perry et al. were the first group to describe intra-articular instillation of antibiotics in 1992 [9]. They used an implantable pump with a catheter from the wound surface, to deliver 200-350 mg of amikacin in a 50mg/ml dilution for 8-15 weeks, to 72 patients with acute infections. Of these patients, 49 underwent debridement and retained their prostheses and 23 had their prostheses removed after the initial debridement. They only reported in detail on a subset of 12 patients (10 knees and 2 hips, median age of 59) with no prior history of infection and with a 37-month follow-up. Local levels of antibiotics were assessed by assaying wound drainage or synovial fluid and ranged from 150 ug/ml to 1688 ug/ml. Serum levels were 10ug/ml, except for one patient whose serum concentration rose to 13ug/ml. Two patients developed recurrent infection, one with the same organism *Staphylococcus aureus (S. aureus)* and the other patient was infected with *Staphylococcus epidermis,* after originally infected with *S. aureus.* In the series of 49 patients who retained their prostheses, 38 patients were infection free, however, follow-up times ranged from 1-58 months.

Fukagawa et al. reported on their experience with 15 patients (16 knees) treated for PJI with stable prostheses [10]. A causative microorganism was identified in eight patients. Patients were treated with open synovectomy, debridement, exchange of polyethylene insert and retained their implant. In the five patients with tumor megaprostheses, the anchors were retained. A Hickman catheter was inserted percutaneously and organism specific antibiotics (if an organism was cultured) were infused into the joint space twice per day until clinical signs of infection resolved, and white blood cell (WBC) count, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) normalized, at which point the catheters were pulled. The mean infusion duration was 20.8 days +/- 11.7 days. Intra-articular antibiotics used were: amikacin (400 mg/day), gentamicin (80mg/day) and arbekacin (200 mg/day). No serum antibiotic levels were reported. All patients also received IV or oral antibiotic therapy for 1-3 months. All patients were considered infection free and clinically healed during the first follow-up period of 46.7 months (±25.7 months). However, four of the five knees treated with tumor megaprostheses developed recurrent infection after a mean of 28.3 (±26.1 months). These patients were treated with intra-articular antibiotics again for 13-22 days and the infection was clear at last follow-up. No local toxicity or infection at the catheter site was reported.

Tsumura et al. [11] reported on the treatment of early knee PJI in ten patients with continuous, concentrated, antibiotic irrigation for 7-29 days. Antibiotics were administered through a Salem double lumen catheter after debridement with implant retention. Eight of the 10 patients were infection free and able to retain the original prostheses. The two failures were the only patients with methicillin-resistant *Staphylococcus aureus* (MRSA). Antibiotics administered were: clindamycin, amikacin, cefotiam, imipenem, arbekacin, piperacillin, cefazolin, ampicillin and vancomycin. No serum or synovial antibiotic levels were reported.

In two recent publications, Whiteside et al. reported on a retrospective cohort of 18 total knee arthroplasty (TKA) patients with recurrent knee PJIs treated with single-stage (10 patients) or two-stage revision arthroplasty (8 patients), including 3 patients that required limb lengthening and soft tissue expansion [12,13]. Intra-articular antibiotic infusion using a Hickman catheter was performed as an adjunct to meticulous debridement. The authors administered 100 mg of vancomycin or 20 mg of gentamicin in 3 mL of saline into the joint space and increased the dosage to 500 mg of vancomycin or 80 mg of gentamicin in 8 ml of saline, every 12 or 24 hours as tolerated, once the wound was stable and dry. Patients were also treated postoperatively with 1 gm of IV vancomycin and 80 mg of IV gentamicin for 48 hours. The intra-articular antibiotics were continued for six weeks, with intra-articular vancomycin levels ranging from 10,233- 20,167 mg/L. Mean serum vancomycin peak and trough levels were 4.1+/- 1.2 µg/mL and 3.3 +/- µg/mL respectively. Three patients had to have a reduction in the antibiotic dose due to excessive rise in the level of antibiotics. Follow-up ranged from 2.3-12 years, with a mean of 6.1 years. One patient had a recurrent, postoperative infection at 13 months. No other patients had clinical or serological signs of infection and no patient was placed on chronic suppressive antibiotics. Similarly, Roy et al. compared synovial concentrations of antibiotics with IV vs. intra-articular administration in a subset of patients in the Whiteside study cohort, and found an average, peak intra-articular vancomycin concentration of 9,242 ± 7,608 mg/L following intra-articular antibiotic infusion compared to an average intra-articular concentration of 6.8 µg/mL following IV administration [14]. These data suggest with reasonable certainty that direct intra-articular infusion of antibiotics offers a significant benefit in treating resistant organisms, but certainly do not rise to the same level of evidence as would a RCT performed at the same center.

Revision after reinfected, two-stage revision total joint arthroplasty is an especially challenging clinical problem and is even more difficult when multiple failures have occurred. The complication rate of using antibiotic spacers is substantial including dislocation, fracture and migration of the spacer with bone loss that must be considered when contemplating a second two-stage exchange procedure. A revision with intra-articular antibiotic infusion may play a role in this scenario to reduce morbidity. Antony et al. described intra-articular antibiotic infusion as an adjunct to single-stage revision for previously failed single- or two-stage revision for knee, hip or shoulder PJI, in 57 patients with a mean age of 65 years [15]. Hickman catheters were used for intra-articular infusion of organism specific antibiotics for approximately 4-6 weeks, once or twice per day without concomitant systemic antibiotics. The intra-articular antibiotic dose administered was determined to be 50% of the serum dose given the enclosed space. Infection eradication was defined as negative culture, and normal ESR and CRP and 89.5% of patients were successfully treated at 11 months follow-up. Synovial levels of antibiotics were not collected.

TABLE 1. Therapeutic range, toxicity, minimum biofilm eradication concentration (MBEC), and minimum inhibitory concentration (MIC) of antibiotics used to treat biofilm-encapsulated bacteria

Antibiotic	Therapeutic Range	Toxic Plasma Concentration	*S. aureus*		*MRSA*		*P. aeruginosa*		*S. epidermidis*		*E. coli*	
			MIC	MBEC	MIC	MBEC	MIC	MBEC	MIC	MBEC	MIC	MBEC
Azithromycin	0.04-1	-			512	5120		2560				
Ceftazidime	<150	-					1-4	2560-5120				
Ciprofloxacin	2.5-4	11.5			0.06->32	256 - 1280	0.25-2	80-1280				
Clindamycin	<0.5	-			0.015 - 0.06	64 - >1024						
Colistin	1-4	-										
Daptomycin	6-10	-	0.25	600	0.125	1014						
Doxycycline	<10	30			0.064 - 0.125	64 - 128						
Erythromycin	0.5-6	12-15	1	6400	0.12 - >256	64 - >1024		2560				
Gentamicin	5-10	12	1	6400	0.06 - 64	1 - >256		512xMIC				
Linezolid	0.5-4	-	1	6400	1 - 2	4 - >1024						
Piperacillin	5-20	-					4-128	>5120				
Rifampicin	0.1-10	204	0.16	40								
Tobramycin	5-10	12-15	1	160-4000	1	≥8000	0.2-16	250-2560	32	≥8000	2	62.5-125
Vancomycin	<5-10	30	2	2000-8000	0.25 - 2	2000-8000			2	1000-8000		

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QUESTION 7: Can debridement, antibiotics and implant retention (DAIR) be utilized in patients with an acute chronic infection of a unicompartmental knee arthroplasty (UKA)?

RECOMMENDATION: In the event of acute infection following UKA, early DAIR can be considered. However, if initial treatment effort results in failure or chronic infection is present, the implanted prosthesis should be removed and a one-stage or two-stage conversion to total knee arthroplasty (TKA) should be performed in combination with antibiotic therapy.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

The main reasons for revision of UKA are loosening, progression of osteoarthritis to another compartment and infection [1]. The incidence of infection after UKA at 0.2 to 1% is lower than that reported after total knee arthroplasty (TKA) [1,2]. A distinctive feature of UKA infection is that both the prostheses and the native cartilage are involved [1]. This is in part attributed to the use of minimally invasive exposures, with less damage to the adjacent soft tissue and sparing of bone and ligamentous structures [3].

In the event of immediate or acute infection following UKA, early irrigation and debridement followed by antibiotic administration can be a proper treatment solution. However, if the initial treatment effort ends up in failure or chronic infection is present, the implanted prosthesis should be removed and a one- or two-stage revision surgery should be carried out [3]. Labruyere et al. reported on failures for nine infected UKA cases managed with one-stage irrigation, debridement and conversion to TKA in combination with three months of antibiotic therapy [1]. Of note, five of these cases first failed DAIR. Kim et al. reported management of five infected UKA cases with two-stage conversion to TKA [3]. Bohm et al. reported two infected UKAs, one of which was managed with one-stage conversion

TABLE 1.Summary of infected UKA cases in the literature

Author/Year	N (infected UKA cases)	Failed DAIR	Treatment	Failures	Follow-up
Labruyere 2015[1]	9	5	one-stage conversion to TKA (9)	0	Median 60 months
Bohm 2000[4]	2 (0.7% infection rate)	?	one-stage (1) two-stage (1)	1 (AKA)	Mean 4 years
Saragaglia 2013[5]	8 (2% of failed UKAs)	?	?	?	?
Kim 2016[3]	5 (0.3% infection rate)	?	two-stage (5)	?	?

successfully and the other was treated with two-stage conversion, ultimately resulting in above the knee amputation [4].

In the setting of UKA, recommendations are weak as only five published papers examine the results of failed UKA, including infection and the rate of infection is very low (Table 1). Two of the infected UKA cases in one study [1] had been post-traumatic infections prior to implantation of the UKA and thus represent more complex scenarios potentially predisposing to treatment failure. There is no literature directly evaluating the role of DAIR in the setting of UKA. However, subsequent failure due to progression of osteoarthritis (OA) occurred in two cases (survival 49%) at an average of three years. Therefore, it may be advisable to proceed with one- or two-stage conversion to TKA at the time of infection in the setting of UKA to minimize the need for additional revision procedures in the future and prevent associated morbidity.

In general, the surgeon should assess prior UKA function, component position and fixation and condition of alternate knee compartments to determine whether retention of implants with DAIR is an appropriate initial treatment in the setting of infection.

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QUESTION 8: Can debridement, antibiotics and implant retention (DAIR) be utilized in the treatment of acute periprosthetic joint infection (PJI) with a megaprosthesis?

RECOMMENDATION: DAIR is a viable treatment option in acute PJI of a megaprosthesis. The effectiveness of DAIR is still unclear due to lack of comparative data among the treatment options and limited evidence to suggest superiority of any one treatment. The treatment decision must be made on a case-by-case basis and account for underlying medical conditions, infection history, organism characteristics and surgical history. DAIR is most appropriate for acute PJI without complicating factors, such as extensive and pervasive infection by a high virulence or resistant organism.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Acute PJI of megaprostheses is a terrible complication and a difficult situation for treatment [1]. Infection rates in patients with megaprostheses have been reported to range from 3% to greater than 30% [1–3]. In principle, the treatment of acute PJI with a megaprosthesis is similar to treatment of other acute PJI, except there is significantly more potential space and a greater soft tissue infectious burden requiring more extensive exposure and debridement [4,5]. The surgical options include DAIR [6–8], one-stage revision surgery [4], two-stage revision with an interval cement spacer [9–11], arthrodesis and amputation [5,8]. Unfortunately, there is limited data on the outcome of these different procedures [1,9]. The lack of comparative data is due to the limited indications for a megaprosthesis as well as the clinical heterogeneity of the affected patients [5]. Additionally, treatment details vary greatly, particularly for DAIR. Specific information on the debridement, the type of irrigation solutions, modular component exchange and local and systemic antibiotic use and duration are generally lacking.

Two-stage revision remains the preferred method for treatment of PJI [8–10]. However, two-stage revision significantly increases surgical and perioperative risks and includes a substantial period of reduced mobility between stages, which has heightened interest in alternative surgical options such as DAIR. DAIR is an attractive option as it may prevent the unnecessary removal of implants, which could result in further bone loss and fracture [6,11,12]. DAIR is also the simpler and less costly procedure with a demonstrated shorter length of hospital stay [13]. The overall goal of attempting DAIR should be to select the cohort of patients in whom successful treatment is most likely.

Sujith et al. summarized the absolute and relative contraindication for DAIR [13]: The absolute contraindications are loose prosthesis, poor soft tissue coverage and compromised bone cement mantle. The relative contraindications are the presence of sinus tracts, methicillin-resistant and methicillin-susceptible *Staphylococcus aureus* (MRSA and MSSA) infection, previously revised joints, immunosuppression, rheumatoid arthritis, polymicrobial involvement, bacteremia, C-reactive protein (CRP) >100 mg/L, erythrocyte sedimentation rate (ESR) >60 mm/h, two or more previous debridements and >3 weeks of symptoms.

The decision to perform DAIR can also be based on the classification of the infection. According to Pilge et al.if intraoperative cultures are positive without other signs of infection (Tsukayama Type I), implant retention is attempted and prolonged systemic antibiotic treatment is recommended. Implant retention should also be attempted with stable arthroplasties in type II or III infections (early postoperative infection or acute hematogenous infection). If there are radiological signs of implant loosening, a one- or two-stage revision must be performed [14,15].

During DAIR, thorough debridement is necessary to improve outcome. All infected and nonviable tissue around a well-fixed prosthesis must be removed. Retained components are irrigated and

scrubbed in an effort to remove biofilm [11,13]. Various antibiotic solutions can be used intraoperatively, including dilute betadine and Dakin's solution. Culture-driven systemic antibiotics are also important for successful treatment and co-treatment with rifampin should be utilized in Staphylococcal PJIs [6]. Prolonged or chronic antibiotic suppression may also be necessary. The use of local antibiotics in addition to the administration of systemic antibiotic agents is an area of consideration. Modular components and the exposed metal of megaprostheses can be covered with antibiotic eluting cement, though there is no clinical evidence comparing the efficacy of such methods versus more simple modular exchange.

The most important factors contributing to treatment failure are longer duration of symptoms, a longer time after initial arthroplasty, the need for multiple debridements, the retention of exchangeable components and PJI caused by MRSA [6,11,12]. One- or two-stage revision should be performed if DAIR fails [11,13].

In general, DAIR is a treatment option for acute PJI with a megaprosthesis with varying levels of success in selected and non-complicated patients. The heterogeneity inherent in these cases makes comparisons difficult and there is always some degree of individualization in choice of treatment.

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QUESTION 9: What factors are associated with the successful treatment of acute periprosthetic joint infection (PJI) using debridement, antibiotics and implant retention (DAIR)?

RECOMMENDATION: The following factors have been shown to be associated with treatment success in acute PJIs treated with DAIR:

- Exchanging the modular components during debridement
- Performing a debridement within at least seven days, but preferably as soon as possible, after the onset of symptoms
- Adding rifampin to the antibiotic regimen, particularly when combined with a fluoroquinolone, in cases of susceptible staphylococci
- Treatment with fluoroquinolones in cases of susceptible gram-negative bacilli

The following factors have been shown to be associated with treatment failure in acute PJIs treated with DAIR:

- Host related factors: rheumatoid arthritis, old age, male sex, chronic renal failure, liver cirrhosis and chronic obstructive pulmonary disease
- Prosthesis indication: fracture as indication for the prosthesis, cemented prostheses and revised prostheses
- Clinical presentation representing the severity of the infection: a high C-reactive protein (CRP), a high bacterial inoculum and the presence of bacteremia
- Causative microorganisms: *S. aureus* and Enterococcoci

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

The success of DAIR depends on multiple host- and implant-related factors, clinical presentation, intraoperative variables, causative microorganism(s) and their antibiotic sensitivities and the antibiotic regimen. It is of note, that the described factors related to treatment outcome in some studies, are not always confirmed by others. Most factors associated with success of DAIR are demonstrated in retrospective studies, entailing a high risk of selection bias, especially for those factors involving certain treatment strategies. Therefore, prospective validation is critical for most of the described variables and differences between cohorts should be taken into consid-

eration in interpreting risk factors. In addition, the success of DAIR depends on the definition of treatment failure and the total duration of follow-up, which also differed amongst the selected studies.

Factors that are consistently shown in the literature to **increase** the chance of treatment success are:

Exchange of Modular Components

The bacterial load detected on polyethylene is higher compared to metal components of prostheses, presumably due to its rough surface that favors the adherence of bacteria [1]. Therefore, exchanging the modular components will reduce the amount of biofilm present on foreign material. Moreover, removing the modular components during DAIR (i.e., femoral head and/or polyethylene component) provides better access to the joint capsule for radical debridement. Tsang et al. reviewed all cohort studies published between 1977 and 2015 on the outcome of DAIR in hip PJI. The success rate of DAIR in studies where all patients underwent modular component exchange was 73.9% (471/637 patients; 95% confidence interval (CI), 70 to 77) compared to 60.7% (245/404 patients; 95% CI, 56 to 65) in patients in whom modular components were retained ($p < 0.0001$) [2]. In addition, Grammatopoulos et al. demonstrated in a cohort of 82 acute hip PJIs a treatment success of 93.3% when modular components were exchanged versus 75.7% when modular component were retained ($p = 0.02$) [3]. Smaller studies confirm the same in acute PJIs of the knee [4,5]. The beneficial effect of modular exchange was also demonstrated as independent predictors of treatment success in large multi-center cohort studies evaluating the outcome of DAIR in hip and knee PJIs caused by methicillin-resistant and methicillin susceptible *S.aureus* ($n = 345$, hazard ratio (HR) 0.65, $p < 0.026$)) [6], streptococci ($n = 462$, HR 0.60, $p < 0.01$) [7] and solely late acute PJIs ($n = 340$, odds ratio (OR) 0.35, $p = 0.02$).

Performing DAIR within at Least Seven Days after the Onset of Symptoms

Several studies demonstrated that the duration of symptoms are significantly shorter in patients who were successfully treated with DAIR compared to patients in whom treatment failed [8–13]. In most studies, the most prominent difference between success and failure is observed using a symptom duration of one week as optimal cut-off [3,10,11,14,15]. Urish et al. demonstrated a treatment success rate of 53.2% in 216 knee PJIs when DAIR was performed within one week after the onset of symptoms. Additional multivariate analysis in this study showed that the chance of failure increased when DAIR was postponed to two weeks after onset of symptoms (HR 1.68), and further increased after four weeks of symptoms (HR 2.34) ($p = 0.002$) [14]. Grammatopoulos et al. demonstrated a treatment success rate of 90.7% in 82 hip PJIs when DAIR was performed within one week after the onset of symptoms versus 75.0% when DAIR was performed after one week ($p = 0.05$) [3]. As the maximum days of symptom duration was not well described in all studies and chronic PJIs are indeed included in some [3,10,12,14], the beneficial effect of debridement within one week may be overestimated in these studies for solely acute PJIs.However, a study performed in 110 patients who had a maximum of 32 days of symptoms indicates the same conclusion [8,9]. These authors demonstrated that for each additional day of postponing DAIR, the odds of implant retention decreased by 15.7% and 7.5% for hip and knee PJI, respectively. In the same study, multivariate analysis showed that performing a DAIR within five days was an independent predictor for treatment success, with an OR of around 0.05 for both hips and knees (95% CI 0.01 to 0.24). These data support the concept that a DAIR should be performed within one week to increase the chance of treatment success, but should preferably be performed as soon as possible.

The Addition of Rifampin in Staphylococci PJI

In the randomized controlled trial performed by Zimmerli et al. in 1998, 24 patients with an infected orthopaedic implant caused by staphylococci and treated with surgical debridement were randomized to antimicrobial treatment with combination ciprofloxacin/rifampin or with ciprofloxacin monotherapy. Adding rifampin to the antibiotic regimen improved treatment success from 58 - 100% ($p = 0.02$)) [16]. Although relatively small in sample size, this study served as the foundation of adding rifampin to the antibiotic regimen in staphylococcal PJI. Thereafter, the benefit of rifampin was primarily demonstrated in observational studies [6,17–19]. In a prospective study including 86 monomicrobial staphylococci knee PJIs treated with open debridement, rifampin-based regimens had a 40% higher treatment success compared to other regimens ($p = 0.01$) [17]. Moreover, the addition of rifampin has shown to be a strong independent predictor for treatment success in multivariate analyses [6,20]. The greatest beneficial effect of rifampin has been shown when combined with a fluoroquinolone, which can be explained by the effectivity of fluoroquinolones against biofilm and by drug-interactions of rifampin with several other antibiotics but not with levofloxacin, the most frequently used fluoroquinolone. In a retrospective study of gram-positive infections treated with DAIR, Tornero et al. demonstrated that rifampin combined with linezolid, co-trimoxazole or clindamycin (which are known to have a drug-interaction with rifampin) was associated with a higher failure rate (27.8%) compared to a combination of rifampicin with levofloxacin, ciprofloxacin or amoxicillin (8.3%) ($p = 0.026$) [19]. The greater benefit of the fluoroquinolone-rifampin combination therapy compared to other antibiotic regimens was also illustrated by Puhto et al. in a study of 113 patients with acute PJI: compared to rifampin-ciprofloxacin, the HR for treatment failure was significantly increased in the rifampin-other antibiotics group (HR 6.0, 95% CI 1.5 to 28.8, $p = 0.014$), and even higher in patients treated without rifampin (HR 14.4, 95% CI 3.1 to 66.9, $p < 0.01$) [20]. In addition, Senneville et al., observed the same in 41 patients with acute *S. aureus* PJI treated with DAIR: treatment success was 93.8% in the fluoroquinolone-rifampin group, 66.7% in the rifampin-other antibiotics group and 57.1% in regimens without rifampin ($p = 0.11$) [21]. Altogether, these data indicate that adding rifampin to the antibiotic regimen, particularly when combined with a fluoroquinolone, is associated with an increased chance of treatment success in acute PJI treated with DAIR.

The Use of Fluoroquinolones in Gram-negative PJI

The protective effect of antibiotic treatment with a fluoroquinolone is demonstrated in two prospective and one retrospective observational study [19,22,23]. In a prospective cohort of 22 patients with early PJI caused by gram-negative organisms, the use of fluoroquinolones was associated with a lower failure rate (7.1%) compared to other antibiotic regimens (37.5%) ($p = 0.04$) [19]. In addition, in a cohort study of 47 cases, treatment with a fluoroquinolone in susceptible gram-negative bacilli was associated with a better outcome ($p = 0.0009$) and was an independent predictor of treatment success (OR, 9.09; 95% CI, 1.96 to 50; p0.005) [23]. Finally, a large retrospective, multicenter study on gram-negative PJI was performed in 16 Spanish hospitals in which DAIR was performed in 72% of the cases (174/242 cases) [22]. The overall success rate of DAIR was 68%, which increased to 79% in gram-negative PJIs treated with ciprofloxacin. In agreement with the previous study, ciprofloxacin treatment exhibited an independent protective effect in the multivariate analysis (HR 0.23; 95% CI, 0.13 to 0.40; $p < 0.001$). In all of these studies, no propensity score matching was performed to correct for possible selection bias. In addition, it should be noted that in most of the performed studies, oral therapy with fluoroquinolones was compared with oral beta-

lactam antibiotics. Questioning the superiority of fluoroquinolones, Grossi et al. demonstrated that treatment with high dose intravenous beta-lactam antibiotics (alone or with the addition of another antimicrobial agent) was not inferior to treatment with fluoroquinolones [24]. Although this study had a relatively small sample size (n = 76) and included both DAIRs and staged revision surgeries, it does provide some evidence for the possibility that alternative intravenous antibiotic regimens and/or combination therapy may be as effective as treatment with fluoroquinolones. More studies are required to confirm this finding.

Factors that are consistently shown in the literature to **decrease** the chance of treatment success are:

Host-related Factors

The importance of host factors in the outcome of patients with a PJI was highlighted by McPherson et al., who described the first grading of the medical and immune status of the host to predict outcome [25]. However, this grading system was not validated in large cohorts of patients who underwent DAIR. For patients managed with DAIR, three large cohort studies in streptococci, staphylococci and late acute PJI identified patients with rheumatoid arthritis (RA) as an important risk factor for failure [6,7]. This high risk for failure in RA patients has been demonstrated in smaller studies as well [10,26,27]. The most pronounced risk was observed for late acute PJIs, demonstrating a failure rate of 74% in patients with RA versus 43% in patients without ($p < 0.001$), and was shown to be an independent predictor for failure in the multivariate analysis, with an OR of 5.1 (95% CI 1.1 – 24.3, $p = 0.04$). Age has been independently associated with worse outcome in a recent large cohort of late acute PJIs, showing that patients older than 80 years old had a significantly higher risk of failure (OR 2.6). In addition, a clear correlation between treatment failure and age has also been described in a large cohort of early PJIs [28]. Male sex [28], chronic renal failure [7,22,29] and liver cirrhosis [29,30] were also identified as independent predictors of failure in patients treated with DAIR. Patients with chronic obstructive pulmonary disease (COPD) showed an increased risk for failure in late acute PJIs only. In this study, COPD was not a significant predictor for failure in the multivariate analysis (OR 2.9, 95% CI 0.99 – 8.68, $p < 0.05$).

Prosthesis Indication

Despite the fact that fracture and revision arthroplasties have a higher predisposition for infection [31–34], these arthroplasties have been associated with a higher risk for treatment failure in acute PJIs as well. Fracture as an indication for the prosthesis has been shown to be associated with DAIR failure in three studies of early acute PJIs [28,29,35] and in one study of late acute PJIs as well. With an average failure rate that is 20 - 30% higher compared to osteoarthritis, fracture as an indication for prosthesis has been shown to be an independent predictor for treatment failure in two studies [29]. The same holds true for revision arthroplasty compared to infected primary arthroplasty, with a failure rate that is 12 - 22% higher [29,36], and even higher in knees [4]. Revision arthroplasty has been shown to be an independent predictor for failure in early acute PJI [29,36]. Only one study demonstrated an increased risk for failure in cemented prostheses, with an OR of 8.7 in the multivariate analysis [29].

Clinical Presentation

Several factors considered as surrogate parameters for the severity of the infection have been associated with treatment failure: a high CRP at clinical presentation [6,23,28,29,37], the amount/percentage of positive intraoperative cultures representing the bacterial inoculum [28,29] and bacteremia/sepsis [7,28,29,38]. In most of these studies, these factors are closely correlated to one another. In case of CRP value, an average cut-off value of > 115 mg/L has been associated with an increased failure rate, depending on the type of infection (late acute or early acute). Notably, late acute/hematogenous infections appear to be associated with worse outcomes compared to early acute/post-surgical infections, especially when the infection is caused by *S. aureus* [6,15,20,37–41].

Causative Microorganism

It has been demonstrated in several studies that an infection caused by *S. aureus* is associated with an increased risk of failure [28,36,42,43]. In a large retrospective cohort of 386 early acute PJIs performed by Löwik et al., the percentage of failure was 17% higher when the infection was caused by *S. aureus* compared to other microorganisms (47.5% vs.30.2%, $p < 0.001$). *S. aureus* infection was also a prominent risk factor for failure in late acute PJIs, illustrated by an OR of 3.52 for *S. aureus* in the multivariate analysis. Methicillin-resistant *S. aureus* (MRSA) infection was associated with an increased risk for failure in a study performed by Cobo et al., but this was not demonstrated as an independent variable in the multivariate analysis [40]. Indeed, Lora-Tamayo et al. clearly demonstrated that MRSA infections have similar failure rates as methicillin-susceptible *S. aureus*, although the time to failure differs [6]. Next to *S. aureus*, overall, poor outcomes have been described for enterococcal PJIs [43–46]. The largest analysis on enterococcal PJI have been performed by Tornero et al., who reported a failure rate of 53% in 94 patients treated with DAIR [45]. Subanalysis demonstrated that infection caused by *E. faecium* have a worse outcome than those caused by *E. faecalis* (72% vs. 42% failure, $p < 0.04$). Indeed, two studies identified the presence of enterococci as an independent risk factor for failure in acute PJI treated with DAIR [43].

Ultimately, a clinical risk score including the most potent factors associated with treatment failure and treatment success should be developed to predict the individual chance of treatment success. One of the main objectives of risk scores would be to identify patients with high failure rate using DAIR. To be of most clinical use, these scores should preferably include preoperative variables only. So far, two articles described a risk score for failure in early acute PJIs (KLIC-score, Fig. 1A) [29] and late acute PJIs (CRIME80-score, Fig. 1B) treated with DAIR. These risk scores can aid in the clinical decision making to choose an alternative surgical approach and/or to intensify the antimicrobial regimen.

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TABLE 1. Literature review of factors associated with successful treatment of acute PJI using debridement, antibiotics, and implant retention

Author, Year	N	PJI	Variables	Failure Rate	Univariate (OR or HR)7	Multivariate (OR or (a)HR)7
Tsang, 2017 [2] Meta-analysis	1296	Early & late	Symptoms≤7 d vs. >7 d Exchange of modular components (yes vs. no)	28% vs. 48%, p = 0.0001 26% vs. 39%, p = 0.0001	-	-
Grammatopoulos, 2017 [3]	82	Early & late	Symptoms≤7 d vs. >7 d Interval since arthroplasty ≤6 w vs. >6 w Exchange of modular components (yes vs. no)	9% vs. 25%, p = 0.05 7.5% vs. 27.5%, p = 0.01 6.6% vs. 24.4%, p = 0.02	-	-
Zhang, 2017 [4]	34	Early & late	Exchange of modular components (yes vs. no)	39% vs. 100%, p = 0.008	-	-
Choi, 2011 [5]	32	Early & late	Exchange of modular components (yes vs. no)	47% vs. 100%, p = 0.001	-	-
Lora-Tamayo, 2013 [6]	345	Early & late	ImmunesuppresionImmunosuppression (yes vs. no) Bacteremia (yes vs. no) Polymicrobial (yes vs. no) CRP Exchange of modular components (yes vs. no) Need of ≥2 debridements (yes vs. no) [2]levofloxacin+rifampin [3]vancomycin+rifampin	71% vs. 43%, p = 0.006 65% vs. 41%, p = 0.001 59% vs. 41%, p = 0.005 NP, p = 0.001 41% vs. 56%, p = 0.004 71% vs. 41%, p = 0.003 NP, p = 0.008 NP, p = 0.02	2.31 2.29 1.76 1.29 0.56 1.98 0.50 0.34	2.23 1.81 1.77 1.22 0.65 1.63 0.42 0.29
Lora-Tamayo, 2017 [7][8]	462	Early & late	[8]Chronic renal failure (yes vs. no) [8]Rheumatoid arthritis (yes vs. no) [8]Immunesuppression (yes vs. no) [8]Revision (yes vs.no) [8]Late post-surgical infection (yes vs. no) [8]Bacteremia (yes vs. no) [8]Exchange of modular components (yes vs. no)	54.5% vs. 40.8%, p = 0.05 64.9% vs. 40.0%, p < 0.01 60.4% vs. 39.9%, p < 0.01 53.6% vs. 38.3%, p < 0.01 62.9% vs. 38.2%, p < 0.01 47.7% vs. 37.9%, p = 0.02 33.0% vs. 51.6% , p < 0.01	1.58 2.23 1.86 1.60 1.41 1.44 0.59	- 2.36 - 1.37 2.20 1.69 0.60
Wouthuyzen-Bakker, 2018 [8]	340	Late	Gender, male vs. female Age, > 80 y vs.≤ 80 y old COPD (yes vs. no) Active malignancy (yes vs. no) RA (yes vs. no) Immunesuppression Immunosuppression (yes vs. no) Fracture (yes vs. no) Revision (yes vs. no) CRP >150 vs. ≤150 mg/L Bacteremia (yes vs. no) S. aureus (yes vs. no) Exchange of modular components (yes vs. no)	49.1% vs. 40.6%,p = 0.11 54.8% vs. 42.3%, p = 0.06 55.9% vs. 43.8%, p = 0.18 51.7% vs. 44.4%, p = 0.04 74.1% vs. 42.5%, p = 0.001 61.5% vs. 42.9%, p = 0.03 70.6% vs. 41.9%, p = 0.02 54.2% vs. 41.7%, p = 0.04 47.9% vs. 41.7%, p = 0.06 56% vs. 39.8%, p = 0.005 53.9% vs. 38.7%, p = 0.005 36.4% vs. 52.4%, p = 0.004		2.02 2.60 2.90 - 5.13 - 5.39 - 2.00 - 3.52 0.35
Urish, 2017 [14]	206	Early & late	Symptoms ≤7 d vs. >7 d S. aureus vs. other	NP, p = 0.004 NP, p = 0.04	1.77 0.63	1.68 0.59
Koh, 2015 [15]	52	Early & late	Early vs. late PJI	18.7% vs. 47.3%, p = 0.04	-	-

TABLE 1. Literature review of factors associated with successful treatment of acute PJI using debridement, antibiotics, and implant retention (*Cont.*)

Author, Year	N	PJI	Variables	Failure Rate	Univariate (OR or HR)7	Multivariate (OR or (a)HR)7
Triantafillopoulos, 2015 [9]	78	NP	Thyroid disease Duration of symptoms MR-staphylococci	68.7%, p = 0.03 p = 0.0001 57%, p = 0.004	-	-
Kuiper, 2013 [10]	91	Early & late	RA (yes vs. no) Symptoms ≤7 d vs. >7 d Early vs. late PJI ESR>60 mm/h CNS vs. others	70% vs. 30%, p = 0.03 26.6% vs. 48.4%, p = 0.02 31% vs. 71.4%, p = 0.04 NP, p = 0.001 69% vs. 28%, p = 0.009	-	1.2-84[1] 1-18[1] 1.1-366[1] 2.2-98[1] 1.8-309[1]
Marculescu, 2006 [11]	99	Early & late	Sinus tract Symptoms >8d	61%, p = 0.002 51%, p = 0.04	2.85 1.79	2.84 1.77
Buller, 2012 [12]	309	Early & late	Symptoms <21 d vs. ≥21 d ESR Previous infection in the same joint (yes vs. no) Resistant-GP vs. others	NP, p = 0.001 p = 0.02 55% vs. 44%, p = 0.009 65% vs. 44%, p = 0.005	-	-
Hsieh, 2009 [13]	154	Early & late	GN vs. GP	73% vs. 53%, p = 0.002	-	-
Tornero, 2016 [16]	143	Early	Suboptimal vs. optimal (rifampin for GP and FQ for GN) antibiotic treatment	31% vs. 8%, p = 0.004	-	4.92
Puhto, 2015 [20]	113	Early & late	Early vs. late PJI Leukocytes > vs. ≤ $10x10^9$/L Ineffective empirical antibiotics vs. effective [4]Rifampin+ciprofloxacin vs. Rifampin+other vs. other	30.8% vs. 54.3%, p = 0.002 50% vs. 24.6%, p < 0.01 60% vs. 33%, p < 0.006 10% vs. 40% vs. 70%, p < 0.01	- R+C vs. R+O: 6 R+C vs. O: 14	- 3.7 3.2 -
Holmberg, 2015 [17]	145	Early & late	Revision (yes vs. no) Rifampin vs. no rifampin	63% vs. 23%, p = 0.02 19% vs. 59%, p = 0.01	-	-
Vilchez, 2011 [38]	65	Early & late	Early vs. late PJI Need of ≥2 debridements	24.5% vs. 58.7%, p = 0.02 NP, p = 0.001		2.57 4.61
El Helou, 2010 [18]	91	Early & late	Rifampin vs. no rifampin	4% vs. 40%, p = 0.03	-	0.11
Zimmerli, 1998 [16][5]	18	Early	Rifampin+ciprofloxacin vs. ciprofloxacin	100% vs. 58%, p = 0.02	-	-
Senneville, 2011 [21]	41	Early & late	Rifampin+FQ vs. other	6% vs. 32%, p = 0.001	-	-
Martínez-Pastor, 2009 [23]	47	Early & late	FQ vs. no FQ for GN PJI CRP > vs. ≤ 15 mg/dL	7% vs. 52%, p = 0.005 50% vs. 17%, p = 0.04	-	9.09 3.57
Tornero, 2015 [29]	222	Early	Chronic renal failure (yes vs. no) Liver cirrhosis (yes vs. no) Femoral neck fracture / revision surgery vs. primary Cemented prosthesis (yes vs. no) CRP > vs. ≤11.5 mg/dL	60% vs. 20%, p < 0.001 48% vs. 21% , p = 0.004 35% / 38% vs. 16%, p = 0.003 25% vs. 19%, p = 0.39 56% vs. 16%, p < 0.001	-	5.92 4.46 4.39 / 4.34 8.71 12.3
Rodriguez-Pardo, 2014 [22]	174	Early & late	Ciprofloxacin (yes vs. no) Chronic renal failure	21% vs. 60%, p < 0.001 NP, p < 0.02	-	0.23 2.56
Grossi, 2016 [24]	35	Early & late	Ciprofloxacin (yes vs. no)	21% vs. 28%, p = 0.65	-	-

TABLE 1. Literature review of factors associated with successful treatment of acute PJI using debridement, antibiotics, and implant retention (*Cont.*)

Author, Year	N	PJI	Variables	Failure Rate	Univariate (OR or HR)7	Multivariate (OR or (a)HR)7
Löwik, 2018 [28]	386	Early	CRP >115 vs. ≤115 mg/L Gender, male vs. female Left-sided prosthesis (yes vs. no) Sepsis (yes vs. no) Ischaemic heart disease (yes vs. no) Fracture (yes vs. no) Gentamicin impregnated beads or sponges (yes vs. no) S. aureus (yes vs. no)	55.2% vs. 30.3%, p < 0.001 46.6% vs. 33.2%, p = 0.08 46.7% vs. 31.1%, p = 0.002 52.1% vs. 35.1%, p = 0.007 50.6% vs. 35.3%, p = 0.013 52.8% vs. 33.3%, p = 0.047 43.0% vs. 23.7%, p = 0.001 50.2% vs. 36.6%, p = 0.022		- 2.03 1.80 - 1.84 - NP NP
Hsieh, 2013 [26]	154	Early & late	RA (yes vs. no)	78% vs. 48%, p = 0.002	-	-
Son,2017 [27]	25	Early & late	RA (yes vs. no)	50% vs. 5%, p = 0.04	-	-
Tornero, 2014 [30]	160	Early	Liver cirrhosis (yes vs. no) CRP > vs. ≤12 mg/dL GN not treated with a FQ vs. treated with a FQ	67% vs. 29%, p < 0.001 47% vs. 29%, p = 0.04 57% vs. 31.5%, p = 0.005	-	12.4 1.06 6.5
Bergkvist, 2016 [35]	35	Early	Hip fracture (yes vs. no)	64% vs. 19%, p = 0.01	-	8.3
Byren, 2009 [36]	112	Early & late	Arthroscopy vs. open S. aureus vs. others Revision vs. primary	53% vs. 12%, p = 0.008 30% vs. 24%, p = 0.05 34.6% vs. 12.8%, p = 0.008	5.4 2.6 2.6	4.2 2.9 3.1
Vilchez, 2011 [37]	53	Early	CRP > vs. ≤ 22 mg/dL Need of 2nd debridement (yes vs. no)	54.5% vs. 16.6%, p = 0.01 75% vs. 18.4%, p = 0.006	-	20.4 9.8
Rodriguez, 2010 [39]	50	Late	S. aureus GN	62.5%, p = 0.01 0%, p = 0.01	3.08 0.46	5.3 0.6
Cobo, 2011 [40]	139	Early	MRSA (yes vs. no)	66.6% vs. 39.6%, p = 0.05	-	None
Tande, 2016 [41]	43	Late		66.6% vs. 39.6%, p = 0.05		
Letouvet, 2016 [42]	60	Early & Late	Number of prior surgeries S. aureus (yes vs. no) Antibiotic treatment < 3 months	p = 0.03 50% vs. 22%, p = 0.02 46% vs. 23.5%, p = 0.01	2.7 3.4	6.3 9.4 20
Soriano, 2006 [43]	47	Early	Enterococcus spp or MRSA vs. others	87.5% vs. 9%, p = 0.003	-	17.6
Kheir, 2017 [44][6]	87	Early & Late	VSE VRE Polymicrobial with enterococci	35% 50% 56%	-	-
Tornero, 2014 [45][6]	203	Early & Late	VSE VRE	41.8% 72%	-	-
Duijf, 2015 [46]	44	Early	Enterococcus sp	34%	-	-

CRP, C-reactive protein; PJI, periprosthetic joint infection; NP, information not provided; MR, methicillin-resistant; ESR, erythrocyte-sedimentation rate; CNS, coagulase-negative staphylococci; GP, gram-positive cocci; GN, gram-negative bacilli; FQ, fluoroquinolone; VSE, vancomycin-susceptible enterococci; VRE, vancomycin-resistant enterococci; RA, rheumatoid arthritis.

[1] Confidence interval 95%.

[2] Sub-group analysis of patients with a post-surgical PJI due to methicillin-susceptible *S. aureus* (MSSA).

[3] Sub-group analysis of patients with a post-surgical PJI due to methicillin-resistant *S. aureus* (MRSA).

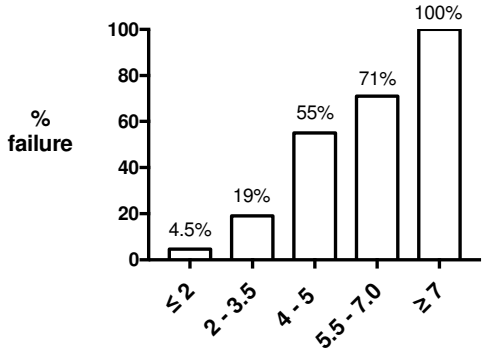
[4] Sub-group analysis of patients with a post-surgical PJI due to staphylococci.

[5] Randomized, placebo-controlled, double-blind trial.

[6] Including patients treated with DAIR and prosthesis exchange.

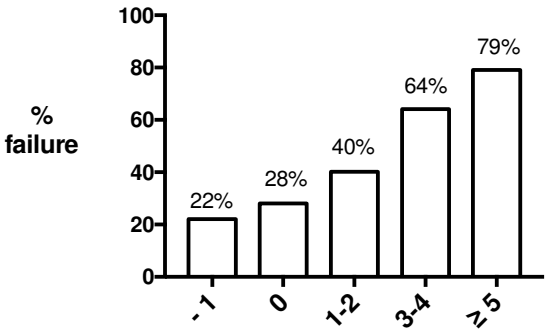
[7] Only depicted when p-value < 0.05.

[8] Only depicting the results associated with overall failure.



K	Chronic renal failure (Kidney)	**2**
L	Liver cirrhosis	**1.5**
I	Index surgery: indication prosthesis: fracture OR revision prothesis	**1.5**
C	Cemented prosthesis	**2**
	CRP > 115 mg/L	**2.5**

FIGURE 1A. KLIC preoperative risk score [19,28]



C	COPD	**2**
	CRP > 150 mg/L	**1**
R	Rheumatoid arthritis	**3**
I	Indication prosthesis: fracture	**3**
M	Male	**1**
E	Exchange of mobile components	**-1**
80	Age > 80 years	**2**

FIGURE 1B. CRIME80 preoperative risk score [19,28]

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QUESTION 10: Does performing a debridement, antibiotics and implant retention (DAIR) affect the outcome of a subsequent two-stage exchange arthroplasty?

RECOMMENDATION: Unknown. Based on the available evidence, it is not known if prior DAIR adversely affects the outcome of a subsequent two-stage exchange arthroplasty.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 93%, Disagree: 6%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

There are several surgical treatment options for periprosthetic joint infection (PJI), including irrigation and debridement (I&D) with modular component exchange and one- or two-stage exchange arthroplasty, with the ultimate choice depending on a number of variables, including chronicity of infection, organism and antibiotic sensitivity patterns, host factors and experience of surgeon. I&D with implant retention has been an attractive strategy in select circumstances as it is less morbid for the patient and less costly to the healthcare system overall. However, the failure rate of I&D is not insignificant, averaging 68% in the literature (61-82%). Following treatment failure of an I&D, the recommendation for subsequent treatment is often a two-stage exchange arthroplasty. The question remains whether the initial attempt at I&D adversely affects the outcome of the subsequent two-stage exchange arthroplasty.

Two earlier studies and one very recent study on this subject seemed to indicate that failure of an initial I&D and modular component exchange leads to a higher than expected failure rates of subsequent two-stage exchange arthroplasty. Sherrell et al. performed a multicenter retrospective review of periprosthetic knee infections treated with a two-stage procedure following an initial treatment

with I&D [1]. Of the 83 knees that had undergone prior I&D, 28 (34%) failed subsequent two-stage revision and required reoperation for persistent infection. With the numbers available, there was no difference between success and failure with respect to age, gender or American Society of Anesthesiologists (ASA) grade. The other earlier study was a retrospective review of 44 patients who had undergone I&D for acute periprosthetic knee infections identified from the HealthEast Joint Replacement Registry and the Minneapolis Veterans Affairs Medical Center (MVAMC) total knee arthroplasty (TKA) database [2]. Of the 25 (57%) patients who failed an attempt at an I&D, 19 went on to an attempted two-stage revision procedure, and in only 11 of these 19 cases (58%) was the two-stage revision procedure ultimately successful. In a very recent retrospective review of 184 PJIs, Rajgopal et al. reported a 23.86% (21/88) failure rate after two-stage exchange following failed I&D compared to 15.62% (15/96) after direct two-stage exchange [3]. The success rate of the subsequent two-stage exchange arthroplasty procedures in all of these series is lower than historical published results, which the authors conclude may be due to the infection becoming more entrenched in the soft tissues and bone.

Two more recent studies on this topic report the opposite findings, namely that I&D before a two-stage exchange does not increase the risk of failure. Brimmo et al. used the California and New York State Inpatient Databases to identify all two-stage exchange revision TKA patients and compared failure rates, as defined as subsequent surgery due to infection within four years, between those with and without prior I&D [4]. Of the 750 patients who underwent two-stage exchange arthroplasty from 2005-2011, 57 (7.6%) had undergone a prior I&D.After four years, the estimated failure rate was 8.7% (95% confidence interval (CI), 1.9%-16.9%) in the group with prior I&D and 17.5% (95%CI, 14.7%-20.4%) in the group without prior I&D. After adjusting for sex, race, insurance, median household income and comorbidities, the hazard ratio for the group with a failed I&D was 0.49 ($p = 0.122$, 95% CI, 0.20-1.20) which the authors indicate revealed a lower risk of failure compared to the group without prior I&D. Nodzo et al. reviewed their single institutional experience of patients who underwent two-stage exchange arthroplasty for PJI of total knee replacements, which included 132 who had not had an I&D and 45 patients who had a prior failed I&D [5]. The success rates between groups were similar at 82.5% and 82.2%, respectively, and the only variable they studied which decreased the odds of reoperation was the use of greater than 2gm of vancomycin in the spacer construct.

As is evident from the current literature, there is no conclusive evidence whether performing a DAIR affects the outcome of a subsequent two-stage exchange arthroplasty. All of the articles included, whether single institution, multicenter or database derived reported on a small number of patients who actually had a two-stage exchange arthroplasty after a failed I&D ($n = 83, 25, 88, 57, 45$) and therefore small differences in accuracy of coding or interpretation of data could potentially sway the results significantly. For those that support the belief that a failed I&D is associated with a decreased success rate for subsequent two-stage exchange arthroplasty, it may not be due to the infection becoming more established in the periarticular tissue, but that it is a patient or organism selection bias/confounding variable, and those individuals that fail an I&D inherently have a higher risk of failing a subsequent two-stage exchange arthroplasty.

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QUESTION 11: How many debridement, antibiotics and implant retention (DAIR) procedure(s) are acceptable in management of patients with acute periprosthetic joint infection (PJI) of a primary arthroplasty before removal of components needs to be performed?

RECOMMENDATION: After one failed DAIR procedure, strong consideration should be given to removal of components.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 13%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

A systematic review of the literature was conducted utilizing the Medline/PubMed (www.ncbi.nlm.nih.gov/pubmed), Embase (www.embase.com), and SCOPUS (www.scopus.com) databases. Studies in which there was a standard protocol for a second surgery other than DAIR (i.e., repeat surgery to remove antibiotic beads or planned multiple irrigation and debridement) were not included in this review.

The majority of the studies reviewed are limited by their retrospective nature, small sample sizes and lack of differentiation between acute postoperative PJI and late-hematogenous PJI. Most researchers viewed failure of DAIR as an indication for a different therapeutic procedure; thus, most studies were limited to a single DAIR. Studies in which multiple DAIRs were performed had given limited insight in their methodology as to why and when a second procedure was performed. Multiple DAIR procedures were only performed in a small portion of the sample size [1,2].

A retrospective review by Triantafyllopoulos et al. attempted to address the appropriate number of DAIR procedures a patient should undergo before resection arthroplasty should be performed. In this retrospective series of 141 patients who underwent DAIR for treatment of a deep periprosthetic infection after primary or revision total knee arthroplasty (TKA) or total hip arthroplasty (THA),

19 patients underwent multiple DAIR procedures [3]. Of the 19 patients who underwent multiple (two or three) DAIR procedures, 10 (52.6%) achieved implant retention with infection control. Of the 122 patients who underwent a single DAIR, 78 (63.9%) achieved implant retention with infection control. All failures underwent prosthesis removal and two-stage reimplantation. The difference in failure rate between those who underwent multiple DAIR and those who underwent a single DAIR was not statistically significant. This study was limited by several factors. The authors included both primary and revision surgeries, as well as a heterogenous mixture of acute postoperative PJI and late-hematogenous PJI. The manuscript also had no clear protocol for which patients underwent repeat DAIR or a different procedure. Furthermore, there was no protocol for patients to undergo additional DAIR or any notation of the timing. Patients who underwent a second DAIR greater than 20 days after the first DAIR had 97.4% lower odds of achieving success compared to patients undergoing the second procedure less than 20 days after the first [3].

A multicenter retrospective analysis by Urish et al. demonstrated 109 out of 216 patients who underwent DAIR after TKA required an additional procedure [4]. Of the 109 failures, 59 underwent repeat DAIR. Ultimately, of the patients who failed initial DAIR, only 28.4% had DAIR as their final procedure; thus, subsequent irrigation and debridement had a failure rate of over 70%.

Another retrospective study compared 64 patients who underwent DAIR (n = 39) versus two-stage revision (n = 25) within three months of primary TKA. Of the 39 patients who underwent DAIR, there were 24 failures (61.5%) and all 24 underwent repeat DAIR [5]. All 24 DAIR procedures failed to control the infection [5]. The DAIR patients underwent on average 3.2 additional surgical procedures (range 1-6) to control the infection whereas the two-stage exchange patients underwent a mean of 2.2 surgical procedures (range 2-4). A further study by Vilchez et al. of 53 THA and TKA patients with PJI treated with DAIR, demonstrated that the need for a secondary DAIR was predictive of failure [6].

The literature demonstrates a second DAIR procedure has, at best, equivalent success as an initial DAIR procedure. In order to avoid additional surgical procedures, resection arthroplasty should be considered after an initial DAIR procedure.

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QUESTION 12: What is the optimal length of antibiotic treatment following debridement, antibiotics and implant retention (DAIR) for acute periprosthetic joint infections (PJIs)?

RECOMMENDATION: The optimal length of antibiotic treatment following DAIR remains relatively unknown as there is considerable heterogeneity regarding the length, dose and administration of treatment. A minimum of six weeks of antibiotic therapy seems to be sufficient in most cases of PJIs managed by DAIR-provided surgical treatment.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Acute PJIs may be treated by DAIR [1,2]. In this setting, antimicrobial therapy is administered at high doses during the postoperative period. The median success rate for DAIR for management of acute PJI varies from 34.8 - 100% [3–23]. However, none of the published reports directly compare the outcome of DAIR in relation to the length of antibiotic treatment.

In addition, the details of antibiotic treatment such as the route of administration, dose and the duration of therapy, appear to be missing. Two studies, though not providing the route of antimicrobial treatment, stated that patients undergoing DAIR in the cohort received at least six weeks and a median of seven weeks (range, 3 to 39 weeks) of antimicrobial treatment [9,10]. Majority of the studies reporting the outcome of DAIR [3,5,7,13–18] used an antibiotic treatment regimen based up the algorithm proposed by Zimmerli et al. [1]. The latter consists of 7 to 14 days of intravenous antibiotics, followed by 3 to 6 months of oral antibiotics with activity against bacteria in biofilm (e.g., ciprofloxacin, adjunct therapy with rifampin).

Four studies report that intravenous antibiotic was used in their cohort, with or without adjunctive oral antibiotics during the course of treatment for a median duration of six weeks [8,12,19,24]. A single study discloses that the patients received oral antibiotics only after the DAIR procedure, with a duration of six weeks to lifelong treatment [2]. The remaining 11 studies used a combination of intravenous, followed by oral antibiotic therapy. In these studies, the median duration of intravenous antibiotic therapy was 6 weeks and among the seven studies which reported the duration of oral antibiotics, the median was 16 weeks (range 9 weeks to lifelong).

TABLE 1.Comparative studies addressing the length of antimicrobial therapy in the setting of PJI managed by DAIR

Ref	Design	N	Etiology	Antimicrobials	Observations
26	Observational, retrospective, one center	112	Various	6 weeks of β-lactams/ glycopeptides, followed by oral tratment	Length of therapy did not predict the likelihood of failure
35	Observational, retrospective, comparative, non-randomized, one center	60	Various (mostly Staphylococci)	Common use of rifampin and ciprofloxacin	A 6-week treatment was non-inferior than a 12-week treatment
36	Observational, retrospective, comparative, pre-post design, one center	50	Various (mostly Staphylococci)	Common use of rifampin and fluoroquinolones	An 8-week treatment was non-inferior than long standard treatments (3-6 months)
37	Obervational, retrospective, comparative,non-randomized, multicenter	87	Various (mostly Staphylococci)	Rifampin-based combinations	Same outcomes for 6-week and 12-week treatments
38	Multicenter Randomised Clinical Trial	63	Staphylococci	Levofloxacin + Rifampin	ITT analysis: 8-week treatment was non-inferior than 3-6 months. PP analysis : a trend towards non-inferiority was observed.

All studies included hip and knee prostheses. N, number of patients included (referring to those managed by debridement, antibiotics and implant retention); ITT, intention-to-treat; PP, per-protocol.

There appears to be a wide variation in the length of treatment, route of administration and the type of antimicrobial therapy that is selected for patients undergoing DAIR. The heterogeneity in the literature and the clinical practice may arise as a result of the fact that there are no reliable clinical or biological parameters that allows clinicians to assess the response to treatment and hence determine the optimal length of antimicrobial therapy [25]. There is a weak signal in the literature to suggest that after a "critical" period of antimicrobial therapy, no further improvement in outcome is encountered by extending the antimicrobial treatment. In fact, some investigators have stated that the length of antimicrobial therapy does not influence the outcome of treatment of PJI patients by DAIR [26]. To the contrary some investigators believe that prolonged antimicrobial therapy is more likely to lead to masking of the infection and a delay in identifying treatment failure [26,27].

There is little literature regarding the optimal route of administration of antimicrobial therapy. Majority of treating clinicians would recommend that patients undergoing DAIR should receive intravenous antimicrobials, at least initially. One observational non-randomized comparative study, concludes that the only factor associated with failure was the selection of oral antibiotics and not the duration of treatment [4]. The majority of studies that advocate the use of a six- to eight-week course of antibiotic therapy, state that intravenous antibiotics for two weeks followed by four to six weeks of oral antibiotics is optimal [27–34].

There are three observational non-randomized comparative studies showing no differences in success of DAIR when long or short course of antimicrobials were used (Table 1). In a study by Bernard et al., that included a cohort of 60 patients managed by DAIR, the success rate among patients treated for six weeks of antimicrobials was not lower than those treated for 12 weeks [35]. In 2012, Puhto et al. published a pre-post comparison of 50 patients with PJI treated for 8 weeks vs. 72 patients who received either 3 (hips) or 6 (knees) months of treatment, showing similar success rates (63 vs.67% in the intention-to-treat analysis, and 89 vs.87% in the per-protocol analysis) [36]. More recently, Chaussade et al. analyzed 87 episodes of PJI managed by DAIR, with similar success rates when patients were treated for 6 or 12 weeks [37]. All three studies included knee and hip cases, all type of organisms with a predominance of Staphylococci and varying antibiotic regimen.

One randomized multicenter study compared an 8-week course of levofloxacin plus rifampin vs.a long course, three of oral therapy for hip PJI and six months of therapy for knee PJI in the setting of Staphylococcal PJI managed by DAIR [38]. Although the number of patients included was low, the non-inferiority hypothesis of the 8-week course was proven in the intention-to-treat analysis (success rate of 73 vs. 58% for the short course and long course groups, respectively; n = 66), and a trend towards non-inferiority was observed in the per-protocol analysis (cure rate of 92 and 95%; n = 44) [38]. The results of the DATIPO study, an ongoing French multicenter randomized clinical trial comparing 6 weeks vs. 12 weeks of antimicrobial therapy for patients with PJI undergoing surgical management, including DAIR, is eagerly awaited.

While the results of high level studies are awaited and based on the evaluation of the available literature, it appears that six to eight weeks of antimicrobial therapy is the ongoing standard for patients undergoing DAIR. There is less evidence regarding the optimal route of administration, with majority of the studies advocating the initial treatment should include intravenous route. The type of antimicrobials is also based on the organisms isolated with studies proposing that antibiotics targeting biofilm, such as rifampin, should also be part of the treatment algorithm.

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QUESTION 13: What is the most effective combination of antibiotics in the treatment of acute periprosthetic joint infections (PJIs) caused by methicillin-resistant *Staphylococcus aureus* (MRSA) that has undergone surgical management with debridement, antibiotics and implant retention (DAIR)?

RECOMMENDATION: We recommend a combination of a parenteral antibiotic plus oral rifampin for one to six weeks, followed by rifampin and a companion highly bioavailable oral drug for additional three months, depending on the susceptibility profile of MRSA, patient tolerability and side effect profile.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 88%, Disagree: 10%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Treatment of MRSA PJI that has undergone DAIR remains challenging. An ideal combination of antimicrobial therapy has not been established. Treatment should take into account antimicrobial susceptibilities of MRSA and tailored accordingly. Whenever possible, rifampin-based combinations should be used, but rifampin alone should never be used due to the rapid development of resistance. Rifampin-based combination therapy regimens have been shown to be effective in eradication of staphylococcal organisms and cure PJIs. A widely used algorithm by Zimmerli and the Infectious Diseases Society of America (IDSA) guidelines recommend a quinolone–rifampin combination for susceptible *Staphylococcus aureus* strains and cure rates of 70 - 100% have been reported [1–3]. The duration of antimicrobial therapy for PJI managed with DAIR has not been well established. We recommend two to six weeks of parenteral antimicrobial therapy in combination with rifampin 300 to 450 mg orally twice a day, followed by rifampin plus a susceptible companion oral drug (such as trimethoprim-sulfamethoxazole, ciprofloxacin or levofloxacin, a tetracycline, fusidic acid) depending on the individual tolerance, side effect profile and antimicrobial susceptibility testing [1,4,5]. Certain highly bioavailable drugs such as fluoroquinolones, rifampin, linezolid and trimethoprim-sulfamethoxazole, reach levels in bone that exceed the minimal inhibitory concentration (MICs) for most organisms [6].

Zimmerli et al. have suggested a duration of therapy of three months for total hip arthroplasties (THAs) PJIs and six months for total knee arthroplasties (TKAs) PJIs [1,3]. Shorter courses of therapy (6 vs. 12 weeks) were studied in PJIs treated with DAIR. However, in this study by Chaussade et al. the presence of MRSA, which comprised only 13.8% of infections, was associated with a poorer outcome (remission in 41.7 vs. 73.3% for other pathogens [7]. Chronic oral suppression with trimethoprim-sulfamethoxazole, minocycline or doxycycline based on in vitro-susceptibilities and individual side effect profile and tolerance may be considered following the above regimens and should be reserved for patients who are unsuitable or refuse further surgical therapy. The duration of chronic oral suppression remains unknown.

While the current IDSA guidelines recommend vancomycin as the primary parenteral agent for treatment of MRSA infections, its utility has been questioned due to increasing reports of heterogeneous resistance, treatment failure, and nephrotoxicity. Vancomycin is not bactericidal against small colony variants (SCV) of MRSA. Moreover, Lenhard et al. showed recently in mixed-population experiments that vancomycin favorably selects for the growth of the SCV subpopulation [6]. Therefore, clinicians should consider glycopeptide combination regimens or alternative antimicrobials in patients with severe persistent MRSA infections in which the SCV phenotype may play a role.

In vitro analyses have identified fluoroquinolones and oritavancin as retaining high levels of vancomycin in vitro against SCVs and β-lactam combinations with daptomycin may offer a new option for combating SCVs [8,9,10]. While optimal treatment for infections caused by staphylococcal SCVs is not known, combination therapy including either rifampin or oritavancin appears to be particularly effective at eradicating intracellular SCVs [11].

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QUESTION 14: What antibiotic therapy (agent, route, dose and duration) is recommended for gram-negative acute periprosthetic joint infections (PJIs) being treated with debridement, antibiotics and implant retention (DAIR)?

RECOMMENDATION: Following surgical intervention (DAIR), gram-negative acute PJI patients should also receive antibiotic treatment for 6 to 12 weeks based on the type of organism. In fluoroquinolone-susceptible cases, the recommended antibiotic agent is a fluoroquinolone.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 83%, Disagree: 11%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

In recent decades, the number of PJIs caused by gram-negative organisms, including multidrug-resistant gram-negatives (GNs), has increased [1]. Several studies have been published on antibiotic treatment of these infections in patients treated with surgical debridement and implant retention (DAIR) [2–8]. Studies have been performed demonstrating the preferred antibiotic agent for treating these infections, but few relate to the preferred route, dose and duration of antibiotic treatment.

Antibiotic Agent for GN PJIs Treated with DAIR

Rodriguez-Pardo et al. performed a retrospective analysis on 242 GN PJIs, including 174 cases (72%) treated with DAIR [2]. The study demonstrated that the use of fluoroquinolones (in this study ciprofloxacin) was associated with the highest success rate of 79% (98 of 124), while the success in the remainder of the patients treated with other antibiotic regimen (e.g., β-lactam or cotrimoxazole) was only 40% (20 of 49). In addition, ciprofloxacin treatment exhibited an independent protective effect in the prevention of subsequent failure in the multivariate analysis (adjusted hazard ratio (aHR) 0.23; $p < 0.001$). In addition to endorsing the use of fluoroquinolones, the latter study also favored the use of combination therapy, as a β-lactam antibiotic combined with a fluoroquinolone or an aminoglycoside as this regiment showed a trend towards better outcome (aHR 0.42, $p < 0.07$). The cohort of patients included in the study were mostly infected with *Enterobacteriaceae* spp. (78%) and some with *Pseudomonas* spp. (20%). The study was not able to glean which of the PJI cases benefited from the combination therapy. Several other smaller studies have been performed, supporting the beneficial effect of fluoroquinolones. Aboltins et al. [3] studied the outcome of 17 consecutive patients with an early GN PJI, mostly polymicrobial in origin (76%), and mainly involving *Enterobacteriaceae* spp (94%). All of these patients were initially treated with β-lactam antibiotics intravenously, and 14 patients were subsequently treated with oral ciprofloxacin. Treatment failure occurred in two patients not treated with ciprofloxacin (median period of follow-up of 28 months). Only one of these failures was caused by a relapse with the same GN, suggesting a cure rate of 100% (14/14) when using ciprofloxacin versus 66% (2/3) when using another oral antibiotic regimen (in these particular cases amoxicillin/clavulanic acid). In addition, a study performed by Jaén et al. (n = 47) and Tornero et al. (n = 21) on GN PJIs treated with DAIR, which were partly based on the same cohort of patients, also demonstrated that the use of fluoroquinolones in susceptible GN was the only factor associated with treatment success in the univariate analysis [4,7,8].

Recently, Grossi et al. [9] demonstrated in 76 GN PJIs that the outcome of treatment with IV β-lactam antibiotics (alone or in combination with another antimicrobial agent) during the whole treatment period (median three months) was similar compared to the use of an oral fluoroquinolone (failure rate 16.7 vs. 22.4%, $p = 0.75$). Although the study of Grossi et al. included both DAIRs and revisions as surgical strategy, outcome remained the same after stratification according to the surgical procedure, suggesting that intravenously antibiotic regimens and/or combination therapy may be as effective as treatment with fluoroquinolones.

The use of alternative oral regimens other than β-lactam, like cotrimoxazole, have been poorly studied in the field of PJI and require further investigation.

Only a few data are available on how to treat multidrug-resistant (MDR) GN in the field of PJIs, but extensive reviews and expert opinions have been published, utilizing the efficacy of carbapenems, combined with tigecycline, colistin or fosfomycin when the microorganism is susceptible [10–13]. Another question in the consensus document elaborates on the efficacy of tigecycline and fosfomycin alone or in conjunction with β-lactam in the treatment of PJI, suggesting that tigecycline or fosfomycin could be considered for the treatment of MDR GN PJI of as a part of a combination regimen when the microorganism is susceptible.In addition, the benefit of adding colistin to a β-lactam for osteoarticular infections caused by MDR, have been reported as well, demonstrating a higher cure rate for combination therapy [14,15].

Treatment Suration, Route and Dosage for GN PJIs Treated with DAIR

Table 1 shows the treatment duration and subsequent failure rate of the above-mentioned studies. Whether a short or long treatment duration was associated with a respectively lower or higher cure rate was not described in most studies. Only Jaén et al. evaluated the difference in outcome between patients treated with more or less

TABLE 1. Overview treatment duration and outcome in GN PJIs solely treated with DAIR

Author, Year	Patients (n)	IV (days)	Oral (days)	Total (days)	Failure %
Tornero et al. 2016 [4]	21	8 (IQR 5-12)#	69 (IQR 45-95)#	ND	14
Grossi et al. 2016 [9]	35	36 (IQR 14-90)*	ND	90 (IQR 89-92)*	23
Jaén et al. 2012 [8]	47	14 (IQR 8-24)	64 (IQR 28-102)	ND	26
Rodriguez-Pardo et al. 2011 [2]	174	14 (IQR 6-23)	58 (IQR 27-90).	ND	32
Zmistowski et al. 2011 [5]	10	ND	ND	ND	30
Aboltins et al. 2011 [3]	17	40 (range, 9 - 79)	365 (range, 30 - 1678).	ND	6
Hsieh et al. 2009 [6]	27	38 (range, 24-52)	49 (range, 28-92)	ND	27

*, duration of treatment included cases treated with revision surgery; #, duration of treatment included gram-positive PJIs; IQR, interquartile range; ND, no data.

than 14 days of IV treatment and treated with more or less than 64 days of oral antibiotic treatment and demonstrated no differences in outcome [8]. Although studies have demonstrated an equal success rate with 6 to 8 weeks compared to the standard 12 weeks of antibiotic treatment [16–20], these studies have been mainly performed in rifampin susceptible staphylococci and cannot be extrapolated to GN PJIs. For this reason, we would still recommend a 6 to 12-week treatment duration (including 1 to 2 weeks of IV treatment), especially in ciprofloxacin-resistant GN. In caseβ –lactam is indicated, it should be administered intravenously throughout the entire treatment period.

No studies evaluated the dosage of antibiotic treatment and its relation to outcome. We propose the recommendations depicted in Table 2.

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TABLE 2. Proposed antibiotic regimen for GN PJIs treated with DAIR

Microorganisms1	IV Regimen	Oral Regimen
Enterobacteriacae, ciprofloxacin susceptible	Ceftriaxon 2 gm QD ± Ciprofloxacin 400 mg TID	Ciprofloxacin 750 mg BID
Pseudomonas spp, ciprofloxacin susceptible	Cefepime 2 gm TID *or* Meropenem 2gm TID *or* Ceftazidime 2gm TID *or* Piperacillin-tazobactam 4.5gr QID ± Ciprofloxacin 400 mg TID *or* Tobramycin 7mg/kg QD	Ciprofloxacine 750 mg BID
Enterobacteriaceae, ciprofloxacin-resistant	Ceftriaxone 2 gm QD ± Tobramycin 7mg/kg QD	IV β-lactam antibiotics during the whole treatment period *Possible alternative* Cotrimoxazole 960 mg TID
Pseudomonas spp, ciprofloxacin resistant	Cefepime 2 gm TID *or* Meropenem 2gm TID *or* Ceftazidime 2gm TID *or* Piperacillin-tazobactam 4.5gr QID ± Tobramycin 7mg/kg QD *or* Colistin 3 million IU TID *or* Fosfomycin 2-4g QID	IV antibiotics during the whole treatment period

DAIR, debridement, antibiotics and implant retention; PJIs, periprosthetic joint infections; QD, four times daily; TID, three times daily; BID, twice daily

± Duotherapy can be considered in patients who have a high risk for treatment failure.

1 In case of multidrug-resistant or extremely drug-resistant gram-negative, the antibiotic treatment should be guided by the antibiogram and preferentially by combining two antibiotics with a different mechanism of action.

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5.3. TREATMENT: ONE-STAGE EXCHANGE

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QUESTION 1: What are the potential advantages of a one-stage exchange arthroplasty?

RECOMMENDATION: The potential advantages of a one-stage exchange arthroplasty are multiple, including a decrease in surgical morbidity and mortality, earlier functional return, decrease in healthcare and global economic costs as well as an increase in health-related quality adjusted life years.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

While multiple studies have been performed evaluating the efficacy of a one-stage or two-stage exchange arthroplasty for periprosthetic joint infection (PJI) [1–13], the majority demonstrated a reduced rate of recurrent infection after a two-stage exchange in comparison to a one-stage exchange, although the comparative value of these results is difficult to interpret given discrepancies in patient comorbidities, bacterial profiles, treatment protocols as well as variances in the definitions of PJIs, clinical success, and failure.

In North America, treatment of PJIs using a two-stage revision procedure remains the most widely utilized and reported method in the literature [14–16]. However, there is no clear evidence that shows superiority of two-stage over one-stage revision in terms of success, eradication of infection or patient satisfaction [1–11,13,16–18]. In addition, one-stage revision has demonstrated multiple advantages in several prognostic and observational studies, particularly within the European literature [1–13].

Depending on the study and follow-up time, one-stage revision procedures have demonstrated a success rate ranging between 75 to 95% [1–5,7–13,17–19]. This is comparable to the reported reinfection rates after two-stage revisions between 9 and 20% of cases [20]. Furthermore, when appropriately performed, one-stage revision can avoid the morbidity associated with multiple surgeries while providing the advantages of reduced total length of stay, overall cost and earlier functional rehabilitation [19,20]. Other advantages include the reduced duration of postoperative systemic antibiotic therapy and systemic antibiotic side effects [19,20].

Despite this demonstrated success of one-stage revisions, it is critical to recognize that this procedure is contingent on strict patient selection criteria and specific operative planning protocols. For example, preoperative identification of the responsible bacterial organism in the synovial fluid is a prerequisite to determine the specific local and systemic antibiotic therapy regimen [3,6,10,11,19]. Also, patients who fail prior one-stage revision, those with an unclear causative pathogen or lack of susceptibility to available antibiotics and those with more extensive infections, may not be candidates for one-stage exchange [20].

In addition to strict selection criteria, several meticulous intraoperative steps, including aggressive soft tissue debridement, meticulous removal of the prior cement material and all hardware, as well as the use of antibiotic-loaded cement for reimplantation, along with specific postoperative antibiotic regimens, are important for success [19]. In a systematic review comparing one- to two-stage exchange, superior outcomes for one-stage revision were reported when performed in this selective patient population [21].

Two recent meta-analyses comparing outcomes for one-stage versus two-stage exchange for patients who have PJIs after both total hip [22] and total knee [23] arthroplasties demonstrated statistically equivalent reinfection rates for both protocols. These findings, were, however limited by the quality of the studies included in the meta-analyses, as well as a relative paucity of studies evaluating one-stage protocols in comparison to two-stage exchange.

Wolf el al. utilized Markov modeling in a decision-tree analysis to suggest a possible superiority of treatment of a one-stage exchange in comparison to a two-stage protocol as it pertains to health-related quality of life years, despite an objective decrease in recurrent infection with a two-stage protocol [24]. Although

the mortality increase in a two-stage protocol was most directly responsible for the predicted advantage of a one-stage protocol in this study, failure of reimplantation in some circumstances, time between procedures and a longer total recovery, were also utility values which favored direct exchange. Although the challenges in conducting an adequately powered randomized controlled trial to properly address this question are multiple, important controversy regarding this topic will likely remain until this is done.

Based on the current evidence, one-stage revision procedures can be utilized as an alternative to two-stage revision for PJIs, with comparable success. However, this may not be a suitable option for all patients with an infected prosthesis. Meticulous operative planning and surgical technique is important to achieve excellent outcomes. Future prospective, randomized, adequately powered, and preferably multicenter studies are necessary to delineate the superiority of a one- or two-stage revision approach for PJIs. It is likely that marked controversy regarding this topic will likely remain until such evidence becomes available.

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QUESTION 2: What are the indications and contraindications for a one-stage exchange arthroplasty for the treatment of chronic periprosthetic joint infections (PJIs)?

RECOMMENDATION: One-stage exchange arthroplasty remains a viable option for the management of chronic PJIs. In patients with signs of systemic sepsis, extensive comorbidities, infection with resistant organisms, culture-negative infections and poor soft tissue coverage, one-stage exchange arthroplasty may not be a good option.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

The evidence for best practice in the management of PJIs is an evolving science with increasing popularity for one-stage revision arthroplasty over recent years. This popularity is mainly driven by a number of studies reporting comparable [1,2], if not better [3] outcomes of one-stage vs.two-stage exchange surgery and the potential for reduced patient morbidity, mortality and socio-economic burden with the former [4–6]. Excellent outcomes for infection-free survival are documented in the literature, especially where strict criteria for patient selection is met. Haddad et al. [3] in 2015 reported their series of 28 highly selected patients undergoing one-stage exchange for chronically infected knee arthroplasties with a 0% re-infection rate at a minimum of three years follow-up. Their cohort

accurately matched the host, local and microbiological criteria proposed in this updated consensus document. Earlier results from Oussedik et al. in 2010 reported a similar success rate of infection-free survival of one-stage exchange arthroplasty of hip patients in the presence of a strict patient selection protocol [7].

Despite these aforementioned studies, there still remains a lack of high-quality literature addressing the subject matter. Hence, in the absence of published randomized controlled trials, many of our conclusions have been drawn from a combination of retrospective and prospective cohort studies and systematic reviews of these.

Early experience of one-stage exchange arthroplasty by Buchholz et al. [8] in 1981 reported an overall success rate of 77% in a large series of 583 patients. In this study, the microbiological profile appeared to play an important role onthe outcomes, with polymicrobial infections and atypical and gram-negative organisms being associated with a higher failure rate. These findings have later been echoed by Jackson et al. [9] in their literature review in 2000, where they concluded that in addition to these factors, infection with methicillin-resistant *Staphylococcus aureus* (MRSA)/methicillin-resistant *Staphylococcus epidermidis* (MRSE) resistant organisms were associated with poor outcomes. It is important to note, however, that despite these reports, evidence from the HELIOS ENDO-Klinik, where a high volume of one-stage procedures are performed (85% of all septic revision), does not consider these factors as absolute contraindications to one-stage surgery and still has presented promising long-term follow-up [10].

Excellent results have also been reported in a number of series, with 92 - 100% infection free survival, where known microbiological susceptibility had been established preoperatively [3,10–12]. Despite this, the importance of predetermined microbiology has also been indirectly questioned by one or more studies recently [13–15]. Buchholz et al. noted best results in negative culture cases, a criterion previously considered an absolute contraindication for the one-stage strategy. Lange et al., in their series of 56 patients report a 91% infection-free period, despite 15 patients having negative tissue cultures. Furthermore, in their series, only one of the five failures had documented negative culture [13]. Hence, it may be proposed that a lack of preoperative microbiological diagnosis may be considered a relative, rather than absolute, contraindication for one-stage exchange arthroplasty.

Host and local factors have also been highlighted as important determinants of outcome of one-stage revision. A study by Goksan et al. in 1992, on a small cohort of 18 cases, reported a 94% success rate with knees, success defined as eradication of infection. Host profile in this series matched some of the indications criteria later set out by the International Consensus Group in 2013 to include the absence of systemic sepsis and gross tissue inflammation. Of the two reported cases of failure, both patients were noted to have severe immunosuppression [16]. In a retrospective study by Wolf et al. [17], their patient cohort was classified using the McPherson classification system based upon host status and local status. Their series concluded better outcomes in terms of infection eradication with two-stage vs. one-stage procedures being performed in the presence of host systemic compromise (95 vs. 33% eradication for McPherson type B + C patients) and local soft tissue and bony compromising factors (95 vs. 0% eradication for McPherson stage 3 patients). More recently, Bori et al. published their series of 19 consecutive one-stage revision hip cases and reported a 95% cure rate. They noted an absence of important bone defects intraoperatively (with only four cases requiring bone grafting) as a potential contributing factor to their successful outcomes [15].

The presence of soft tissue defects and sinus tracts also appear to have a negative impact on outcomes in some studies with a 27% reinfection rate (6 out of 22 cases) [18]. Similarly, of the five recurrent infections in the series by Lang et al., three patients had soft tissue lesions in the form of a sinus tract at initial presentation and one had an abscess. It is important to note, however, that despite these reported findings, Jenny et al., in an earlier series of 47 patients documented an 87% infection-free survival period at 3 years despite a large number of their cohort of patients (43%) presenting with a fistula. In their series, only two patients with a sinus tract subsequently fell into their reinfection group [19]. Hence, it may be proposed that a discharging fistula is, in itself, not an absolute contraindication to one-stage exchange arthroplasty, a conclusion also drawn by Raut et al. [20].

It may be concluded that one-stage exchange arthroplasty remains a plausible option for the management of chronic prosthetic joint infections in a selected group of individuals with the prospect of promising results for infection-free survival of the revised prosthesis. Much of this evidence, however, is based upon analysis of prospective and retrospective observational studies. Furthermore, the fact that outcomes following one-stage exchange are affected by multiple factors, it is often difficult to assess the impact an individual criterion has. There is no doubt that stronger conclusions may be drawn in the future following results from established randomized controlled trials that are underway in the United Kingdom, United States, and elsewhere. In the meantime, we offer the following as indications and relative contraindications for one-stage exchange arthroplasty.

Indications for One-stage

Host/Local

- Non-immunocompromised host
- Absence of systemic sepsis
- Minimal bone loss/soft tissue defect allowing primary wound closure
- Microbiology
- Isolation of pathogenic organism preoperatively
- Known sensitivities to bactericidal treatment

Relative Contraindication to One-stage

- Severe damage of soft tissues where the direct closure of the joint and the wound is not possible. A complex sinus tract which cannot be excised along with the old scar.
- Culture-negative PJI, where the causative organism and its susceptibility are not known.
- No radical debridement of infected soft tissues or bone is possible (for whatever reason).
- No local antimicrobial treatment is possible (for whatever reason).
- No proper bone stock exists for the fixation of the new implant.

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QUESTION 3: Is there a role for single-stage exchange arthroplasty in acute periprosthetic joint infections (PJIs) of cementless total hip arthroplasties (THAs)?

RECOMMENDATION: Yes. Single-stage exchange arthroplasty can be employed to treat patients with acute PJIs of cementless THAs.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Debridement and retention of implants, single-stage revision and two-stage revision are all described treatment options in the management of PJIs [1]. Since the 1970s, when Buchholz introduced the concept of single-stage revision arthroplasty as an alternative to two-stage revision for PJIs, multiple authors have published similar encouraging results on single-stage revision for infected THA [2–4]. With shorter total hospital stays, less risk of perioperative complications and lower overall healthcare costs, single-stage revision has been considered an attractive treatment option for the devastating complication of hip PJIs [5].

Single-stage exchange arthroplasty for acute PJIs in cementless THAs is a unique situation with pros and cons. On the one hand, the acetabular and femoral components may not have had time to fully osseointegrate. This not only facilitates extraction of implants without incurring significant bone loss, but also allows for the use of "primary type" components for the reimplantation portion of the procedure [6]. On the other hand, one of the primary tenets and keys to the success of Bucholz's original one-stage exchange arthroplasty was the preoperative identification of the infecting organism to help guide the choice of microbe-directed antibiotic cement during the reimplantation of components. In the case of standard "cementless" revision arthroplasty, this is not feasible. As a result, more recently, some surgeons have employed adjunct techniques to achieve similar supra-therapeutic concentrations of antibiotics into the periarticular space during a cementless single-stage revision hip arthroplasty [7,8].

The literature on the topic of one-stage exchange arthroplasty is quite heterogenous, specifically in regards to inclusion criteria, infecting organisms, surgical technique and length of follow-up. Therefore, reaching a definitive conclusion for the role of one-stage exchange arthroplasty in the treatment of acute PJIs of cementless THAs is challenged by the limited available data [6–10]. We identified three clinical studies which reviewed their results of cementless one-stage exchange arthroplasty for acute PJIs of THAs. In a multicenter, retrospective series of 27 patients, Hansen et al. demonstrated a 70% success rate of component retention at a minimum follow-up of 27 months and a mean follow-up of 50 months. However, 4 of the 19 patients required further operative debridement to obtain control of the infection, indicating that an isolated one-stage exchange arthroplasty was successful in only 15 of the 27 patients (56%) [6]. In a study by Wolf et al., which included 24 acute THA infections treated with one-stage cementless exchange arthroplasty, eradication of the infection was achieved in 75% (18/24) at two years mean follow-up [9]. Unfortunately, the study with the longest mean follow-up of 8.6 years only included 6 patients who had undergone one-stage cementless exchange. While they reported no cases of reinfection, they had very strict inclusion criteria for deciding on the one-stage exchange (e.g., negligible pus, healthy patients, no evidence of acute systemic infection) and their infecting organism profile only included *Staphylococcus epidermidis* and one case of *Clostridium,* so the applicability of their results must be interpreted in this light. Similarly, the one study that investigated cementless one-stage exchange arthroplasty for chronic PJIs of THAs by Yoo et al. reported component retention in 10 of 12 patients (83%) at a mean follow-up of 7.2 years, but excluded all patients with PJIs caused by methicillin-resistant *Staphylococcus* aureus (MRSA) [11].

As mentioned earlier, one of the keys to the historical success of the one-stage exchange arthroplasty was the ability to deliver supra-therapeutic concentrations of antibiotics into the periarticular space, which is not feasible in standard cementless two-stage revision arthroplasty. Two authors have developed novel techniques to provide adjunct antimicrobials locally in the hopes of improving their infection-free survival.

Using antibiotic-impregnated allograft bone during single-stage revision for PJI, Winkler et al. showed no recurrence of infection in 34 of 37 (92%) of their patients at a mean follow-up of 4.4 years. They calculated supra-therapeutic concentrations of vancomycin in the drainage fluid up to three days postoperative without systemic adverse renal effects and demonstrated that the antibiotic-impregnated grafts had similar incorporation as the normal allografts [7]. Whiteside and Roy introduced a new concept of antibiotic infusion within the periarticular space after single-stage revision for PJIs using Hickman lines, and by this means they have achieved no reinfections and complete clinical eradications of infection in their 21 cases at five years mean follow-up [8].

Considering the fact that the evidence available to address this question is based on retrospective small case series with heterogenous methodologies, the level of recommendation is moderate at best. Taken as a whole, it appears that single-stage revision for acute PJIs may achieve eradication of infection in approximately 70% of patients, which is superior to many reported rates of success for irrigation/debridement and implant retention in the same setting [6]. Furthermore, this technique limits the perioperative morbidity, surgical complexity and healthcare costs associated with a two-stage exchange arthroplasty, and as such, should be strongly considered in the setting of acute PJIs of a THA.

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QUESTION 4: Does the morbidity and mortality differ between single-stage and two-stage exchange arthroplasty?

RECOMMENDATION: Putting aside the effect on successful treatment of periprosthetic joint infections (PJIs), it is logical that a single surgical procedure puts patients at lower risk for both mortality and morbidity compared to a two-stage exchange arthroplasty that involves two separate operations.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 83%, Disagree: 13%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

PJIs are associated with major patient morbidity and mortality. Browne et al. [1] put this in context with a contemporary comparison of two-stage revision hip arthroplasty to major non-orthopaedic surgery. In their study of over 10,386 patients, implant removal and spacer placementhad a 30-day readmission rate of 11.1% and a 90-day mortality rate of 2.6%. Major complications were found in 15.3% of the patients. Ninety-day mortality rates were significantly higher compared with carotid endarterectomy, prostatectomy and kidney transplant (odds ratio (ORs) between 2.1 and 12.5; $p < .0001$). Readmission rates at 30 days were significantly higher than all other groups including coronary artery bypass grafting and Whipple procedures (ORs between 1.4 and 8.2; $p < .0001$). A recent analysis of a large, prospectively collected, national database has also suggested that revision total knee arthroplasty (TKA) for PJIs is associated with increased postoperative morbidity and mortality in the first 30 postoperative days relative to non-infectious revisions [2].

Traditionally, it has been considered that a two-stage revision strategy may be the gold standardfor the management of PJIs as this allows for a more targeted antimicrobial plan; however, it also exposes the patient to the risks of an additional procedure [3]. Historically, studies have concentrated on the successful eradication of infection as an end-point for comparing one and two-stage surgery. Considering reinfection, several recent systematic reviews have been published that show equivalence in terms of infection eradication for single and two-stage exchange [4–8].

Morbidity

Putting the success of eradication of infection aside, morbidity other than reinfection has generally been rarely reported. Although there are limited qualitative studies that deal with the quality of life of the patients undergoing revision arthroplasty for PJIs, Moore et al. [9] found that deep PJIs impacted all aspects of patients' lives. Two-stage revision had a greater impact than one-stage revision on participants' well-being, because the time in between revision procedures led to long periods of immobility and related psychological distress. However, within the two-stage literature, there is marked difficulty in the interpretation of the data presented and what actually constitutes morbidity for the patient. Gomez et al. [10] raised several important points for discussion, and they highlighted the attrition of patients during the interval period in the two-stage process. Of their 504 cases of PJIs (326 knees and 178 hips), 18% failed to proceed to the second stage. The main reason given was that the patient was unfit for the surgical procedure. Clearly this sub-group represents a major morbidity for the patients concerned and may not be included in other reported results.

With regards to hip surgery, a recent systematic review and meta-analysis published by Kunutsor et al. [6] found that there have been no randomized controlled trials comparing one-stage and two-stage revision hip procedures. All included eligible studies were non-randomized longitudinal cohort studies, which were predominantly retrospective in nature. Very few studies in this systematic review contained morbidity (other than reinfection) as an outcome measure. De Man et al. sought to assess and compare functional outcomes in hip PJIs managed by both strategies [11]. They undertook a retrospective analysis and compared 22 single-stage and 50 two-stage revisions to a control group, who were revised for aseptic loosening. They demonstrated no statistically significant differences in Harris Hip Scores (HHSs), limping and use of support between the single-stage and control groups. Choi et al. performed a retrospective analysis of 17 single-stage and 44 two-stage revisions and found no significance differences in HHS or UCLA activity scores [12]. Klouche et al. found no significant differences in aretrospective analysis of 38 single-stage and 46 two-stage revisions between the two groups in terms of pre- and postoperative Merle d'Aubigné scores or complication rates [13]. Oussedik et al. performed a prospective study comparing 11 single-stage with 39 two-stage revisions and found that the HHS and visual analogue scale satisfaction scores were significantly higher in the single-stage group at a mean of five years postoperatively. They also found that the single-stage patients had a significantly greater improvement in their HHS scores and found that patient satisfaction was also statistically in favor of the single-stage procedure [14]. Reporting of morbidities in the remaining 98 individual studies was too infrequent to draw any significant conclusions.

With regards to knee surgery, the results of another systematic review of 10 single-stage and 108 two-stage studies comprising 5,552 participants also failed to find any studies which used morbidity as a primary outcome measure [5]. Using postoperative clinical outcomes from the studies, neither single- nor two-stage strategies for knee PJIs displayed superiority. Median postoperative range of motion for single-stage revision was 97.5 degrees (range, 93.8 to 100.5 degrees) and for a two-stage revision was 97.8 degrees (range, 93.7 to 104.0). Both median postoperative Knee Society knee scores and Knee Society function scores also showed no statistically significant differences.

Mortality

While clearly mortality is a very definite end-point, the causes for it can be multi-factorial and not always directly attributed to the PJIs and their treatment. When reanalyzing the papers from recent systematic reviews for hip and knee PJIs (with mortality as an outcome), establishing differences between a single- and two-stage approach is extremely difficult [5,6]. A minority of studies featured information about mortality. The upper limit of follow-up duration, where death was considered relevant, or was linked to the revision surgery in the manuscript, ranged from 14 days to 15 years [15,16]. Given that death was rarely a measured outcome, the variation in patient selection (some studies excluded patients who died), the absence of an "unrelated mortality" definition, and the variation in follow-up, meaningful pooled analysis from these studies was not possible. Comparison is also difficult even among studies using one revision strategy: Buchholz et al. found a mortality of 2% (patients) relating to "overall management" with up to nine-year follow-up in 640 single-stage hip revisions [15]. In contrast Raut et al. found an attributable mortality of 0% in their 183 single-stage hip revisions with an "unrelated mortality" of 7.7% (14 patients) [16]. One of the included papers by Wolf et al. used a Markov expected-utility decision analysis for which they derived a mortality rate of 0.52% (3 of 576) for single-stage and 2.5% (8 of 321) for two-stage revision based on 18 published papers [17]. The other reviewed articles were no clearer for two-stage revision or for either strategy in knee PJI revisions. Registry data may be a source of crude mortality; however, the joint registry annual reports of England (including Wales, Northern Ireland and the Isle of Man), Australia, Norway, Sweden, Finland, Canada and New Zealand currently do not publish mortality data for revision subgroups [18–23].

Another method of analyzing mortality rates following single and two-stage exchange, which clearly has some limitations, is to present a data summary of published reports that include 50 or more patients and where mortality is documented (see below). As can been seen in these series, there is marked overlap of the mortality ranges, but the highest mortality is evident with a two-stage exchange. The heterogeneity of the available data is far from robust to undergo meaningful meta-analysis.

One-stage mortality range - 4.4 to 11.4%

Buchholz et al. [24] N = 640 with 90 deaths recorded at mean 52 months follow-up = 8.1%

Loty et al. [25] N = 90 with 4 deaths reported at mean 47 months follow-up = 4.4%

Miley et al. [26] N = 100 with 11 deaths recorded at mean 48.5 months follow-up = 11%

Raut et al. [16] N = 123 with 14 deaths at mean 93 months follow-up = 11.4%

Two-stage mortality range - 2.9 to 25.7%

Chen et al. [27] N = 57 with 5 deaths at mean 67.2 month follow-up = 8.7%

Haddad et al. [28] N = 50with 2 deaths at mean 5.8 years follow-up = 4.0%

Hsieh et al. [29]N = 99 with 3 deaths at mean 43 months follow-up = 3.0%

Romanò et al. [30] N = 102 with 3 deaths at mean 48 months follow-up = 2.9%

Toulson et al. [31] N = 132 with 34 deaths at mean 64.8 months follow-up = 25.7%

Ibrahim et al. [32] N = 125 with 19 deaths at mean 5.8 years follow-up = 15.2%

In conclusion, based on the available studies to date, single-stage revision surgery (when suitable) is associated with lower morbidity and mortality rates. However, the data to support this statement is

weak and larger, prospective, multicenter clinical trials are needed. Of note, two prospective randomized trials are currently recruiting with the aim to compare single- and two-stage revision surgery in the United Kingdom and North America with outcome measures including reinfection, mortality and patient reported outcomes [33].

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5.4. TREATMENT: TWO-STAGE EXCHANGE, SPACER RELATED

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QUESTION 1: What are the indications for the use of non-articulating vs. articulating spacers during resection arthroplasty of the hip or knee?

RECOMMENDATION: Articulating spacers appear to provide better range of motion and less functional limitations to the patients undergoing resection arthroplasty and should be used whenever possible. The indications for the use of non-articulating spacers during resection arthroplasty include patients with major bone loss, lack of ligamentous integrity (knee) or abductor mechanism (hip) that places these patients at elevated risk for dislocation or periprosthetic fracture and patients who have major soft tissue defects in whom motion is protected to allow better wound healing.

LEVEL OF EVIDENCE: Strong

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

RATIONALE

There is no clear consensus on the ideal type of spacer for management of periprosthetic joint infections (PJIs) of the hip and knee. Articulating spacers have been shown to be associated with improved range of motion, better function and also with the ability to facilitate ease of dissection at the second stage [1–5]. Citak et al. [6] reported superior functional outcomes with the use of articulating spacers when compared to static spacers.

Della Valle and colleagues recently demonstrated in a multicenter randomized controlled trial (American Association of Hip and Knee Surgeons (AAHKS) abstract) that articulating spacers for hip are associated with reduced lengths of hospital stay after both the first and second stage. Furthermore, they demonstrated improved range of motion of the knee at one year in the articulating spacer group (113 vs. 100 degrees ($p = 0.033$)) and a more significant improvement from preoperative and postoperative range of motion (18 vs. 3 degrees($p = 0.045$)).

The cost of articulating spacers as well as complications demonstrated with these have been highlighted [7–10]. However, these studies are heterogeneous and are predominantly retrospective case series. Citak et al. [6] observed that surgeon-made articulating spacers were more likely to fracture compared to preformed spacers despite having equivalent functional outcomes and infection eradication rates.

Dislocation rates of hip articulating spacers have been reported to range from 6.4 - 17.5% [5,7,9,11]. Dislocation was significantly higher in designs without an acetabular component or those implanted without cement in the acetabulum [7]. This finding is likely design related. Biring et al. reported a 3% dislocation rate with the prosthesis with antibiotic-loaded acrylic cement (PROSTALAC) spacer and satisfaction scores of 90.5 points at 10 - 15 years mean follow-ups [12]. A total of 44% of the group treated by Tsung et al. experienced such encouraging results with the custom-made articulating spacer (CUMARS) based on the Exeter stem that they opted to not have the second stage [13]. The incidence of periprosthetic fractures has been reported to be up to 11.4% with the use of mobile spacers [9].

Several authors have attempted to compare the results of static and articulating spacers in the knee [1,2,4,14]. However, there is a paucity of high quality evidence. Choi et al. [15], Johnson et al. [14], Chiang et al. [2] and Park et al. [1] found that non-articulating spacers were associated with more bone loss (in keeping with the conclusion of Della Valle et al.), increased rates of patella baja, lower Knee Society scores and range of motion (ROM) and required the use of more extensile approaches at the time of reimplantation. These studies are mainly case series and likely subject to selection bias, as patients with more important bone loss at the time of resection arthroplasty are also more likely to have undergone revision to a static spacer.

More recently, Faschingbauer et al. [16] reported a 9.1% fracture rate and an overall 15% rate of complications in 133 patients treated with static knee spacers. Lichstein et al. [17] reported a 94% eradication rate (in the presence of 25% drug resistant organisms), 100° median ROM after reimplantation and Knee Society Scores similar to those published in two recent systematic reviews [18,19]. Neither Voleti et al. [19] nor Pivec et al. [18] were able to identify significant differences between articulating ($n = 1,934$) and non-articulating ($n = 1,361$) spacers with respect to eradication of infection, complication rates or knee function following implantation. The former study [19] did, however, identify improved knee motion among patients with articulating spacers.

The current evidence does suggest improved function, better patient satisfaction and reduced lengths of hospital stay when an articulating spacer is used during resection arthroplasty compared to non-articulating spacers. In the absence of high level data, we recommend that articulating spacers be used in patients undergoing resection arthroplasty whenever possible. There are, however, circumstances when an articulating spacer is not likely to function well, which include patients with a lack of collateral ligaments in the knee,or with absent abductor mechanisms in the hip. These circumstances place these patients at increased risk for spacer dislocation. In addition, massive bone loss may also preclude the use of articulating spacers as fixation of the spacer may be suboptimal in the first place or its use may result in an elevated risk for periprosthetic fracture. There are also other circumstances when surgeons prefer to immobilize the joint with the use of a non-articulating spacers, which may allow for better healing of the wound.

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QUESTION 2: What are the indications for interim cement spacer exchange or repeat irrigation and debridement (I&D) instead of reimplantation?

RECOMMENDATION: Interim cement spacer exchange and/or repeat I&D may be performed, instead of reimplantation, in the presence of persistent infection and/or mechanical complications.

LEVEL OF RECOMMENDATION: Limited

DELEGATE VOTE: Agree: 97%, Disagree: 0%, Abstain: 3% (Unanimous, Strongest Consensus)

RATIONALE

Two-stage exchange arthroplasty remains the most utilized surgical treatment for the treatment of chronic periprosthetic joint infections (PJIs). However, there are occasions when the antibiotic cement spacer may be exchanged, or an I&D performed, and the reimplantation delayed [1]. The reason for these additional surgical procedures may include the inability to control infection or when potential infection is encountered during an intended reimplantation.

The rationale behind this spacer exchange practice is to deliver a further "new load" of local antibiotics as a strategy to treat the persistent infection [2,3]. Alternatively, an I&D at this stage is hypothesized to reduce the microbial bioburden. Although these practices seem intuitively rational, there is little to no published literature on the outcomes of interim spacer exchanges or additional irrigation and debridement. These additional procedures also carry marked morbidity and affect the patient journey, with Gomez et al. reporting that 17.3% of these patients never undergo reimplantation and 11.9% require more than one spacer [1]. It therefore remains unknown whether interim spacer exchange confers any benefit versus conventional two-stage exchange or in comparison to altered inter-stage antibiotic treatment.

George et al. recently presented a series of 416 two-stage exchanges for PJIs, of which 59 (17%) had an interim spacer exchange performed [4]. On assessment of Delphi treatment success, two-year and five-year success rates were 77% and 66% in the exchange group versus 86% and 77% in the non-exchange group. Their spacer exchange group had a lower infection-free survival adjusted hazard ratio (aHR) 10.69, 95% confidence interval (CI) 1.02-2.81; p = 0.039. Similar findings were presented by Goswami et al. in a retrospective study of 75 interim spacer exchanges and 352 matched controls undergoing conventional two-stage exchange at mean 3.5-year follow-up [5]. They found 31.1% of the interim exchange cohort failed treatment after eventual reimplantation, with a significantly lower treatment success compared to matched patients who underwent conventional two-stage exchange (p = 0.045).

Current indications for an additional spacer exchange or I&D include persistent infection, wound-related problems, draining sinus or mechanical complications such as spacer dislocation or fracture. However, there is also no gold standard diagnostic method demonstrating eradication of joint infection or for optimal timing of reimplantation. Several studies have identified metrics that are useful in determining if there is a persistent infectious state prior to reimplantation. Histological analysis, synovial fluid cell counts, serum D-dimer, leukocyte esterase (LE), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) have all been investigated [6–12].

Feldman et al. evaluated the ability of frozen section histology to identify ongoing infection [13]. They concluded that >5 polymorphonuclear (PMN) cells per high power field (HPF) had 100% sensitivity and 96% specificity for the detection of infection. On the contrary, in a cohort of 54 patients, Cho et al. evaluated the role of PMN cell count in frozen sections at reimplantation in total knee arthroplasties (TKAs) [12]. They identified 15 patients with 5 to 20 PMNs per HPF during reimplantation. At a minimum follow-up of two years, they reported 100% eradication of infection, casting doubt on the role of frozen sections. Furthermore, George et al. demonstrated limited utility of this method for ruling out infection, given a sensitivity of only 50% (CI, 13 - 88%) [14]. False-positive frozen section results can potentially arise in patients with the use of dynamic spacers in hips, which may result in debris that accentuates inflammation seen in frozen sections, thereby making conclusions from frozen section, unreliable in such scenarios.

ESR, CRP and joint aspiration have also been evaluated in this context [8,15]. However, there is no convincing evidence to establish their roles in diagnosing persistent infection or in determining if reimplantation is indicated. Ghanem et al. attempted to define cut-off values for ESR and CRP that improve clinical differentiation between aseptic failure and periprosthetic infection prior to revision total hip arthroplasty [16]. They published that an ESR threshold of 30 mm/h has a sensitivity of 94.3% and a CRP threshold of 10 mg/L had a sensitivity of 91.1% for infection. When combining ESR and CRP cut-offs for a positive diagnosis, this increased the sensitivity to 97.6%. However, when calculated by receiver operating curve (ROC) analysis, the predictive cut-offs equated to 31 mm/h for ESR and 20.5 mg/L for CRP.

Zmitowski et al. evaluated 129 patients undergoing two-stage arthroplasty who had an aspiration before their second-stage procedure [6]. Persistent infection was defined as a positive aspirate culture. In 33 cases (25.6%) that were classified as persistent PJIs, patients had significantly elevated PMN % (62.2 vs. 48.9%; p = 0.03) and white blood cell (WBC) counts (1,804 vs. 954 cells/μL; p = 0.04). Although statistically significant differences were noted, diagnostic accuracy for persistent PJIs was <60% for all variables, except synovial WBC counts.

In another retrospective study of 76 infected TKAs treated with two-stage exchange, Kusuma et al. evaluated the role of serological tests for determining eradication of infection during two-stage exchanges [8]. They concluded that while the ESR, CRP and synovial fluid WBC count decreased in cases where infection control was achieved, these values frequently remained elevated. The ESR remained persistently elevated in 54% of knees and the CRP remained elevated in 21% of knees where the infection had been controlled. Despite their inability to identify any patterns in these tests indicative of persistent infection, they proposed that synovial fluid WBC counts as the best test for confirmation of infection control.

Furthermore, Janz et al. investigated the effectiveness of synovial aspiration in resection arthroplasty hips for detecting persistent infection in patients undergoing two-stage revision total hip arthroplasty (THA) [10]. Diagnostic performance of the synovial aspiration

of these hips achieved a sensitivity of only 13% and a specificity of 98%. They concluded that aspiration is of limited diagnostic validity and cannot reliably detect or rule out infection. However, they highlighted the fact that a positive aspiration culture had a high diagnostic performance.

Recently, serum D-dimer tests have been proposed as promising tests for diagnosing PJIs [7]. The study evaluated the role of D-dimer in detecting the presence of infection at the time of reimplantation. Out of five patients with raised D-dimer levels at the time of reimplantation, two had a positive culture from samples taken during reimplantation and subsequently failed. It is worth mentioning that both ESR and CRP values were normal in these two patients.

As previously mentioned, there is no gold standard test for PJIs. After spacer insertion and a period of antibiotic treatment, infection control is expected and laboratory and clinical signs are expected to improve.

In the setting of a failure to improve or if there is ongoing active infection at the time of planned reimplantation, a repeated irrigation, debridement and spacer exchange may be considered. Further research is essential to establish effective tests that prove eradication of PJIs and therefore determine if reimplantation should be performed. The role of several tests, such as elevated ESR and CRP, synovial WBC, and PMN % as well as serum D-dimer are helpful in determining whether reimplantation can be carried out but are not absolute determinants. A combination of these tests, clinical suspicion, completion of antibiotic therapy and careful evaluation of MusculoSkeletal Infection Society (MSIS) criteria [17] should be used to determine if a repeated cement spacer exchange may be indicated. Repeated I&D of an implanted spacer, without antibiotic spacer exchange, does not seem to have any evidence and is generally considered a suboptimal approach in this setting.

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QUESTION 3: Should the antibiotics placed in a cement spacer be tailored to the sensitivity of the infective organism?

RECOMMENDATION: Antibiotics added to cement spacer during resection arthroplasty should be tailored towards the causative organism and its susceptibility. In case of culture negative periprosthetic joint infections (PJIs), consideration should be given to the addition of a broad-spectrum antibiotic to the cement spacer to cover the most potential pathogens causing PJI.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

The literature was reviewed to identify all publications related to the above question. The systemic review revealed 12 publications with clear information about tailored local antibiotics in bone cement spacers. The majority of the papers were retrospective studies with a relatively low number of patients in each report. One study by Hsieh et al. contained 99 patients, which was the largest cohort [1]. There were two review articles from the same group [2,3]. Kiniet al. reviewed the available literature that consisted of 17 publications related to hip infections and 18 studies related to PJIs of the knee. They did not find clear evidence related to the issue of antibiotics

added to cement, but believed that the literature is supportive of the concept that the antibiotics added to cement should be tailored towards the causative organism, if preoperative cultures were successful in isolating the infecting organism and determining the antibiotic susceptibility [2]. Sukeik et al. concluded that the type of local antibiotics added to the cement or otherwise should be safe, thermostable, hypoallergenic, water soluble, have an adequate bacterial spectrum and be available as a sterile powder [3]. Kooet al. also suggested that antibiotics selected for cement spacer delivery should correspond to the sensitivity of the pathogens and be thermostable [4]. Nevertheless, novel delivery techniques may overcome this problem by microencapsulating antibiotics in alginate beads without affecting elution, handling properties and mechanical strength of the cement [5].

Even though there are no recommended diagnostic protocols adequate to exclude infection persistence prior to reimplantation, blood tests and synovial fluid aspiration before surgical treatment of PJIs can be helpful [2,3,6–10]. Aspirates are cultured and the results of microbiological diagnostics, including the causative organism and the specific antibiotic sensitivity, determine the treatment strategy where consultation of a microbiologist plays a crucial role [1,4,6,11–16].

Local antibiotic concentration at the site of infection can far exceed those obtained by systemic antibiotics alone and can remain well above therapeutic requirements for a longer period of time [1]. The objective is to deliver a high concentration of local antibiotics against the causative pathogens [2]. The choice of antibiotics is based on results of bacterial culture obtained from the preoperative aspiration or tissue specimens from around the joint [1,13,16]. Once the antibiotic susceptibility profile of the microorganisms is analyzed, a designated microbiologist should prepare a specific tailored combination of local antibiotics for use in the bone cement spacer [6], considering the patient allergy profile and medical conditions, particularly renal function [17,18]. If the infective organism cannot be identified preoperatively or infection is identified during a presumed aseptic revision, then a broad-spectrum empiric combination of antibiotics is used in an attempt to avoid development of resistance [1,2,13,15,19]. We have provided a list of all available antibiotics, the range of doses to be used in cement spacers and the organisms that they can target (Table 1).

TABLE 1. Available antibiotics and anti-fungals which can be used in spacers

Antibiotic Group	Type of Antibiotic	Activity Against	Dose per 40 gm cement (in grams)
Aminoglycoside	Tobramycin	Gram-negative bacteria such as *Pseudomonas*	1 to 4.8
Aminoglycoside	Gentamicin	Gram-negative bacteria-*Escherichia coli, Klebsiella* and particularly *Pseudomonas aeruginosa.* Also aerobic bacteria (not obligate/ facultative anaerobes)	0.25 to 4.8
Cephalosporin, 1st gen	Cefazolin	Gram-positive infections, limited gram-negative coverage	1 to 2
Cephalosporin, 2nd gen	Cefuroxime	Reduced gram-positive coverage, improved gram-negative coverage	1.5 to 2
Cephalosporin, 3rd gen	Ceftazidime	Gram-negative bacteria, particularly *Pseudomonas*	2
Cephalosporin, 4th gen	Cefotaxime	Gram-negative bacteria, no activity against *Pseudomonas*	2
Cephalosporin, 5th gen	Ceftaroilne	Gram-negative bacteria, no activity against *Pseudomonas*	2 to 4
Fluoroquinolone	Ciprofloxacin	Gram-negative organisms including activity against *Enterobacteriaciae*	0.2 to 3
Glycopeptide	Vancomycin	Gram-positive bacteria, including methicillin-resistant organisms	0.5 to 4
Lincosamide	Clindamycin	Gram-positive cocci, anaerobes	1 to 2
Macrolide	Erythromycin	Aerobic gram-positive cocci and bacilli	0.5 to 1
Polymyxin	Colistin	Gram-negative	0.24
β-lactam	Piperacillin-not available Piptzobactam	Gram-negative bacteria (particularly *Pseudomonas*), Enterobacteria and anaerobes	4 to 8
β-lactam	Aztreonam	Only gram-negative bacteria	4
β-lactamase inhibitor	Tazobactam	Gram-negative bacteria (particularly *Pseudomonas*), Enterobacteria, and anaerobes in combination with Piperacillin	0.5
Oxazolidinones	Linezolid	Multidrug-resistant gram-positive cocci such as MRSA	1.2
Carbapenem	Meropenem	Gram-positive and gram-negative bacteria, anaerobes, *Pseudomonas*	0.5 to 4
Lipopeptide	Daptomycin	Only gram-positive organisms	2
Antifungale	Amphotericin	Most fungi	200
Antifungal	Voricanazole	Most fungi	300-600 mg

One study suggested that the custom-made cement spacer that contains specific antibiotics targeted towards the infective organism(s) should be made after consultation with a microbiologist or infectious disease specialist [6]. Antibiotics like gentamicin, vancomycin, ampicillin, clindamycin and meropenem can be used as a combination based on organism susceptibility [4,6,14]. Even in cases of multi-resistant germs like methicillin-resistant *Staphylococcus aureus*/methicillin-resistant *Staphylococcus epidermidis* (MRSA/MRSE), it was possible to achieve a 100% infection control rate when the local antibiotic therapy was tailored towards the infecting organism(s) [11]. It is, however, a known fact that antibiotic elution from spacers decreases over time. Studies have shown that bacterial colonization of spacers can occur with increasing in situ time [18,20–22]. Antibiotic cement spacers, thus, play a role for a finite period of time and should be removed at some point.

Another question that remains is whether antibiotics should be added to cement, if used, during reimplantation surgery and, if added, whether the antibiotics should be tailored towards the infective agent. This question has been answered comprehensively elsewhere in the consensus document, citing all the supportive literature. It is, however, our opinion that the addition of targeted antibiotics to cement, if used during reimplantation, may also play a role in reducing the incidence of subsequent failure.

In conclusion, based on a review of the available evidence, it is recommended that the type of antibiotics added to the cement spacer should be targeted towards the infective organism(s) and their susceptibility as determined by preoperative culture. In cases of culture-negative PJIs, strong consideration should be given for the addition of broad-spectrum antibiotics to cement spacers that have activity against the most common organisms causing PJIs.

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QUESTION 4: Which antibiotic(s) should be added to a cement spacer in patients with periprosthetic joint infections (PJIs) caused by multiresistant organisms?

RECOMMENDATION: In the case of PJIs caused by methicillin-resistant *Staphylococcus* aureus/methicillin-resistant *Staphylococcus epidermidis* (MRSA/MRSE), vancomycin should be added to the bone cement spacer. In vancomycin-resistant strains, such as vancomycin-resistant Enterococcus (VRE), or in multiresistant gram-negative PJI cases, individual decision making is mandatory based on the known susceptibilities. Consultation with a microbiologist/infectious disease specialist is strongly recommended.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 99%, Disagree: 0%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Multidrug resistant (MDR) pathogens in the context of periprosthetic joint infections (PJIs) are MRSA, MRSE or VRE and multidrug-resistant gram-negatives (MRGN).

Most PJIs are caused by gram-positive cocci, including *Staphylococcus* species [1], and in some reports methicillin-resistant organisms account for up to 74% of PJIs [2]. For the treatment of PJIs caused by MRSA, vancomycin is usually used for antibiotic therapy and commonly incorporated into bone cement as well as intravenous treatment [3]. The successful clinical control of chronic PJIs due to methicillin-resistant organisms varies from 48 - 89% [4,5] in the hip and 60 - 74% [6,7] in the knee when vancomycin is used in two-stage exchange arthroplasty.

The optimal combination of antibiotics in polymethyl methacrylate cement is not known. Most surgeons prefer to add between two to four grams of vancomycin and a similar dose of an aminoglycoside, such as gentamicin or tobramycin, to the cement. The addition of dual antibiotics to cement has several advantages including a postulated synergy between vancomycin and gentamicin against gram-positive bacteria [8,9] and an improved antibiotic elution from the spacer [10,11]. Moreover, this antibiotic combination results in a decreased risk of bacterial growth on the surface of the cement spacer, which could be detrimental to thecontrol of the infection [10]. Systemic toxicity as a result of elution of antibiotics from cement spacers, though rare, can occur. Thus, it is important to ensure that the renal clearance of the patient and the viscosity of the cement, which affects antibiotic elution, is considered when forming the spacer during resection arthroplasty. Renal toxicity of vancomycin is a potential risk and renal function should be monitored [11,12]. However, Hsieh et al. noted no systemic adverse effects after using high doses of vancomycin and aztreonam in bone cement in 46 patients with a PJI of the hip [13]. Also, Springer et al. reported no systemic adverse effects from the use of high doses of vancomycin and gentamicin in cement spacers in a series of 36 knees with PJIs [14].

Regarding susceptible gram-negative bacteria, third-generation cephalosporins [15], carbapenems [16–19] and monobactam antibiotics [13] have strong activity. They retain their antibacterial capacities after being added into bone cement, but they exhibit different antibacterial durations even when the same antibiotic dose has been used. The kinetics of antibiotic release from bone cement depends on the penetration of dissolution fluids into the polymer matrix and subsequent diffusion of the dissolved drug from the cement [20]. Consequently, the limiting factor that determines the antibacterial activity of the cement is the efficiency of antibiotic elution.

The published literature on the topic of what antibiotics should be added to cement spacers for management of PJIs caused by resistant organisms is not well-established. A few reports exist related to management of PJIs caused by MRSA and MRSE with less literature related to the management of PJIs caused by multi-resistant gram-negative organisms. Numerous factors need to be considered when adding antibiotics to cement, including the renal function of the host, the antibiogram of the organism, the type of cement being used, the allergy profile of the host and so forth. In addition, other patient comorbidities, duration and type of intravenous/oral (IV/PO) antibiotics after spacer placement and the quality of bone and soft tissues should be taken into consideration.

The objective of adding antibiotics to cement spacers is to allow for high elution of antibiotics into the affected joint that will reach beyond the organism minimum inhibitory concentration while avoiding potential for systemic drug toxicity [14,21]. It is important to note that on occasion alternative antibiotics may be added to cement spacers based on the allergy profile of the patient.

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QUESTION 5: What are the contraindications to using antibiotics in a cement spacer?

RECOMMENDATION: With the exception of a scenario in which a patient has a history of severe adverse reaction to each of the thermally-stable antibiotics intended for use in cement spacers in the treatment of prosthetic joint arthroplasty, there are no definite contraindications to using antibiotics in a cement spacer.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

There are no prospective studies directly comparing the use of cement spacers with and without antibiotics. A small randomized controlled trial by Cabrita et al. assessed patients with vancomycin-loaded spacers versus no spacers [1]. The infection rate and multiple outcomes were significantly improved with the use of an antibiotic-loaded spacer; however, it is impossible to separate benefits of the presence of the spacer versus impregnation of the spacer with antibiotics. A retrospective assessment of 120 cases found no benefit in infection eradication with the use of an antibiotic-loaded spacer but also noted no adverse effects from their use [2].

There are no studies that describe a benefit from omitting antibiotics from the cement spacer used to treat infection.

There are multiple case reports relating to nephrotoxicity associated with the use of aminoglycosides and other antibiotics [3–13]. Recommendations include monitoring renal function and other clinical parameters and consideration of spacer removal as soon as possible in the case of ongoing renal dysfunction. Of all of these reports, two papers recommend avoiding aminoglycoside antibiotics in patients at risk of developing renal impairment [12]. Infection has been acknowledged as a risk factor in renal impairment and the relative contributions are unknown. Hypersensitivity to piperacillin/tazobactam has also been observed [14]. Vancomycin has also been associated with systemic adverse reactions when included in the cemented spacers [10,15]. This suggests that specific antibiotics may need to be avoided in the cement spacer on a case-by-case basis, but it does not suggest that antibiotics should be avoided in their entirety.

With the exception of a history of life-threatening allergic reaction to a specific antibiotic [15], no published studies or reports are recommending an outright contraindication to the addition of antibiotics to the cement of a spacer in the treatment of infection. There is a hypothetical scenario of a patient who has a history of severe adverse reactions to each of the thermally-stable antibiotics described for use in cement spacers in the treatment of prosthetic joint arthroplasties that could constitute a contraindication.There are no published case reports of this scenario.

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QUESTION 6: Does the use of surgical drains reduce the effectiveness of antibiotic-impregnated cement spacers?

RECOMMENDATION: The current literature indicates that the use of surgical drains does not reduce the overall effectiveness of antibiotic-impregnated cement spacers.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 85%, Disagree: 10%, Abstain: 5% (Super Majority, Strong Consensus)

RATIONALE

Recent literature suggests there is no inherent benefit to using closed suction drainage (CSD) following primary total joint arthroplasty (TJA) [1–3]. Additionally, many of these studies have concluded that CSD is costly and can negatively influence early functional outcomes in primary TJA patients [4]. However, the utility of CSD in revision TJA has yet to be determined. In contrast to primary TJA, revision TJA has been shown to result in greater blood loss as well as increased wound complications and hematoma formation because of its greater operative complexity [5]. The potential value of using CSD for revision TJA lies in the belief that lowering the tamponade-like effect of hematoma formation may lead to improved wound healing and better functional outcomes. A randomized prospective study comparing groups with CSD and those without CSD demonstrated no significant differences in patient satisfaction, pain levels and early functional outcomes for patients undergoing aseptic revision [6]. Still, there is much debate in regards to how CSD plays a role in periprosthetic joint infections (PJIs) following revision TJA and whether CSD should be used when there is placement of an antibiotic-laden cement spacer.

The influence of CSD on local antibiotic concentrations following cement spacer placement is not well-studied. In 2006, Hsieh et al. reported on a series of 46 patients who underwent two-stage hip revisions. Drains were placed for seven days and used to measure antibiotic levels (vancomycin) from day one to seven [7]. A comparison was made between serum antibiotic levels and antibiotic levels in the affected joint at a mean of 107 days postoperatively following the first-stage surgery. Antibiotic concentrations were noted to be above the minimal required level showing substantial elution despite drain placement. Again in 2009, Hsieh et al. assessed the drain fluid of 42 patients who had gentamicin spacers following infected total hip arthroplasty. They concluded that antibiotic levels in the drain fluid were also at clinically effective levels [8].

In 2009, Anagnostakos et al. reported on a series of 28 patients who had infected total hip arthroplasties. Hip spacers were used in 17 patients and beads were used in 11 patients. Drains were placed until there was less than 50mL of daily output and local concentrations of vancomycin and gentamicin were assessed at that time. The study showed that that beads showed better elution rates than spacers after drains [9]. This may have been the result of increased surface area when using beads as the vector for antibiotic elution. Additionally, a study by Regis et al. examined seven patients who had infected total hip arthroplasties. Drains were placed for 24 hours and drainage fluid was obtained at 1 and 24 hours, respectively. Antibiotic concentration and bactericidal titers were analyzed against staphylococcal strains. Vancomycin and gentamicin concentrations were bactericidal at 1 and 24 hours, showing that the drains had not reduced the efficacy of elution [10]. Similarly, Balato et al. enrolled 18 patients in a prospective study where 10 total hip and 8 total knee arthroplasty patients underwent two-stage revisions with the placement of drains for 48 hours. Samples were collected at 15 intervals over the course of the 48-hour period. Antibiotic concentrations were highest at 1 hour and lowest at 48 hours. However, bactericidal concentrations of antibiotics were found at 48 hours, providing evidence of effective elution after drain placement [11].

Additionally, a study by Bertazzoni et al. reported similar findings to those mentioned above. They used drains to measure the concentrations of a vancomycin and gentamicin combination spacer in 12 patients for a 24-hour period following revision hip and knee arthroplasty [12]. They concluded that the concentrations of gentamicin and vancomycin were bactericidal, exerting a strong inhibitory effect against methicillin-resistant *Staphalococcus aureus* and coagulase-negative staphylococci strains. This demonstrated that drains had not reduced the efficacy of the antibiotic spacer elution rates. Another study by Isiklar et al. reported similar findings for spacers with vancomycin alone [13]. Kelm at al. used a novel study design (using both in vivo and in vitro analysis) to examine the spacers of ten patients who had infected total hip arthroplasties [14]. Initially, spacers were implanted and drain fluid was assessed every 24 hours for 7 days. Spacers were explanted at a mean of 9 weeks and they were analyzed for antibiotic concentrations left over. It was determined that after explantation there was still a sufficient concentration of antibiotics to inhibit bacterial growth even after drain placement for up to 7 days. In contrast, further research using animal models, where drains can be left in place for much longer, have measured antibiotic release up to 7 weeks [15].

The above studies illustrate that the presence of a drain does not diminish the minimal bactericidal concentration of antibiotics eluted from an implanted antibiotic-laden spacer. There was no evidence available to support a claim that the presence of drains increased the risk of reinfection. However, in a retrospective review of 82 patients who underwent two-stage revisions, Jung et al. noted that increased drain output was an independent risk factor for prolonged wound drainage and this indirectly was a significant predictor of wound infection [16].

In summary, although suction drains will remove joint fluid and therefore remove antibiotics from the joint, this is probably only a proportion of the total eluted antibiotic. Once the drains have been removed altogether, elution should continue locally at effective levels as justified by the aforementioned studies.

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QUESTION 7: Is there a role for intraoperative autoclaving and reuse of an infected prosthesis as a spacer during resection arthroplasty?

RECOMMENDATION: Multiple studies have demonstrated that the reuse of autoclaved prosthetic components during knee resection arthroplasty did not compromise the eradication of an established infection. Though a viable option, there are potential legal implications associated with the reuse of autoclaved components and a proper standard for autoclaving of these components is also not known. Reuse of autoclaved components in resection arthroplasty, particularly for the knee, may be suitable in scenarios when proper dynamic spacer components are not available or for economic considerations.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 82%, Disagree: 12%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

There are multiple types of antibiotic spacers reported in the literature. They are intended to preserve potential space for later reimplantation and to deliver high dose local antibiotics from the cement. Spacers are either static or dynamic. Dynamic spacers allow for motion in the hip and knee, limb length preservation in the hip and at least partial weight bearing during the treatment period. Dynamic hip and knee spacers may be constructed from new components, cement molds, or from autoclaved components matched to new tibial or acetabular inserts. The literature on static vs. dynamic knee spacers is mixed, but there is some evidence that eventual range of motion may be superior with the use of dynamic spacers [1].

The reuse of an autoclaved femoral component (AC-FC) as a spacer in prosthetic knee infections was first described by Hofmann et al. [2]. The clinical data from several subsequent studies supports the reuse of an AC-FC (Table 1), though they are Level III to IV evidence studies and are subject to being underpowered. Hofmann et al. reported on a 2- to 12-year experience using an AC-FC, demonstrating that 44 of 50 patients (88%) had successful reimplantation and were infection-free at latest follow-up [2]. Lee et al. reported that 19 of 20 patients were successfully treated using an AC-FC articulating against antibiotic cement [3]. Anderson et al. reported 25 consecutive knees treated with an AC-FC spacer and found a 4% failure rate with excellent motion and knee scores at final follow-up [4]. Emerson et al. compared patients treated before 1995 with a static cement spacer to patients treated after 1995 with an AC-FC dynamic spacer [5]. At final follow-up, the patients with AC-FC achieved a significantly better mean range of motion (107.8 vs. 93.7°), while there was no statistical difference in reinfection rate: 9% for AC-FC vs. 7.6% for static spacers. Chen et al.reported on a series of 18 patients: 10 treated with AC-FC and 8 treated with static cement spacers [6]. Similar to Emerson et al., they reported better eventual mean range of motion in the AC-FC group (94.5°) vs. the static cement spacer group (74.3°), with no statistical difference in reinfection rate. Jämsen et al. presented a retrospective series of 34 knees: 24 treated with AC-FC and 10 treated with cement spacers that were manually molded [7]. The authors described slightly better functional scores with AC-FC without increasing the risk for reinfection. Kalore et al. reported on a retrospective comparison of AC-FC vs. new femoral components and polyethylene vs. molded cement components in 53 patients [8]. The infection control rates were 66%, 87.5% and 63%, respectively, a difference that was not statistically different in this relatively small sample size. Importantly, the implant cost for the AC-FC group averaged $932 compared to about $3,500 for the other two groups.

To our knowledge, there is only one study on reuse of hip components in resection arthroplasty. Etienne et al. first reported the surgical technique to reimplant the autoclaved femoral stem or

TABLE 1. Summary of clinical studies

Study	Number of Knees	Autoclaving Protocol	Type of Femoral Component	Type of Tibial Insert	Follow-up Mean (Range)	Reinfection
Emerson [5]	48 Knees Study Group (AC spacer): 26 Control Group (Static spacer): 22	AC of FC (undetailed protocol)	Metal-on-PE cemented spacer	New PE insert	Study: 3.8 years (2.6-6.4) Control: 7.5 years (2.8-12.7)	Study: 2/26 (7.7%) Control: 2/22 (9%)
Cuckler 2005 [14]	44 Knees	AC of FC and PE insert for 10 minutes	Metal-on-PE cemented spacer	Autoclaved PE insert	5.4 years (2-10)	1/44 (2.27%)
Hofmann 2005 [2]	50 Knees	AC of FC (undetailed protocol)	Metal-on-PE cemented spacer	New PE insert	73 months (24-150)	6/50 (12%)
Huang 2006 [15]	19 Patients (21 Knees)	AC of FC and PE insert (undetailed protocol)	Metal-on-PE cemented spacer	Autoclaved PE insert	52.2 months (30-102)	1/21 (4.76%)
Jämsen 2006 [7]	32 Knees Study Group (AC Spacer):22 Control Group (Static Spacer):8	AC of FC and PE insert (undetailed protocol)	Metal-on-PE cemented spacer	Autoclaved PE insert	Study: 25 months (2–68) Control: 49 months (2-86)	Study: 2/22 (9%) Control: 2/8 (25%)
Pietsch 2006 [16]	33 Knees	AC of FC and PE insert (undetailed protocol)	Metal-on-PE cemented spacer	Autoclaved PE insert	28 months (12-48)	3/33 (9%)
Anderson 2009 [4]	25 Knees	NA	Metal-on-PE cemented spacer	New PE insert	54 months (24-108)	1/25 (4%)
Kalore2012 [8]	53 Knees Study group (AC Spacer): 15 New FC and PE insert (NFC): 16 Cement-on-Cement (SMCs): 22	FC scrubbed with betadine, then AC (undetailed protocol)	Metal-on-cement spacer	-	39 months Study: 73 months (37-105) NFC: 19 months (12-32) SMC: 32 months (14-56)	Study: 2/15 (13.3%) NFC: 1/16 (6.25%) SMC: 2/22 (9%)
Kim 2013 [17]	20 Knees	AC of FC at 137°C for 7 minutes	Metal-on-PE cemented spacer	New PE insert	22.3 months (14-60)	2/20 (10%)
Lee 2015 [3]	19 Knees	AC of FC at 132°C for 30 minutes	Metal-on-cement spacer	-	29 months (24-49)	1/20 (5%)
Chen 2016 [6]	18 Knees Study Group (AC Spacer): 10 Control Group (Static Spacer): 8	AC of FC at 137°C for 7 minutes	Study Group: Metal-on-cement spacer Control: Static Spacer	-	Study: 32 months (24-46) Control: 40.8 months (25-56)	Study: 2/10 (20%) Control: 1/8 (15%)

AC, autoclave; FC, femoral component; PE, polyethylene; SMCs, Silicon molded compnents

an inexpensive femoral stem with a new acetabular liner [9]. They published excellent results in 31 of the 32 patients; however, information on the number of patients receiving a resterilized stem and details of the autoclaving protocol were lacking.

There are questions about the ultimate sterility of autoclaved components because of the few studies directly examining the technique. Lyons et al. cultured swabs from six explanted femoral components both before and after a 45-minute autoclave cycle at 121°C [10]. Autoclaving was able to kill the majority of multiple bacterial species of both the planktonic and biofilm phenotypes on the surface of smooth cobalt and chromium (CoCr) material. The six sterile components were then inoculated with various organisms and the tests were repeated; again, no organisms grew after autoclaving. Additionally, electron microscopic analysis of the inoculated specimens demonstrated a dramatic decrease in biofilm after autoclaving. However, the study used relatively immature biofilms (only 24 hours of growth), whereas biofilm formation in vivo likely occurs over multiple days, if not months, on an implant surface. Leary et al. reported that autoclaving at 121°C for 30 minutes was not able to remove biofilms of *Staphylococcus aureus* or *Staphylococcus epidermidis* from the surface of CoCr discs, but that pre-treatment with a 4% chlorhexidine gluconate scrub brush did successfully remove all biofilm [11]. Additionally, in a more recent study, Williams et al. evaluated different flash autoclave temperatures and durations to remove monomicrobial and polymicrobial biofilms of eight days of maturation [12]. Although ten minutes of autoclaving at 132°C rendered all biofilm nonviable by culture, residual biofilm did remain on the titanium materials studied. The clinical importance of remaining nonviable biofilm is unclear, especially when translating these results from titanium material to the CoCr implants used with AC-FC. The use of 4% chlorhexidine gluconate scrub, as shown by Leary et al., may solve this potential problem [11].

All series in this area are small and subject to Type II error; however, the clinical literature taken as a whole consistently suggests equivalent infection eradication between the different strategies, including use of an AC-FC. Additionally, the laboratory study by Lyons et al. demonstrates the effectiveness of autoclaving at a microbiological and microscopic level [10] and the addition of a chlorhexidine scrub prior to autoclaving may further eliminate the potential for nonviable biofilm remnants [11]. While the available clinical evidence and cost-effectiveness of AC-FC make it an intriguing treatment option, many hospitals are restricting the reimplantation of hip and knee components after autoclave resterilization. The Centers for Disease Control and Prevention (CDC), Association of perioperative Registered Nurses (AORN), health care institutions, implant companies and medical consultation teams are understandably hesitant to temporarily reuse implants for medical, legal and financial reasons [10]. In 2016, a directive released by the Department of Veterans Affairs stated that nonbiological implantable devices are not to be sterilized by flash autoclave and should be used primarily in cases of emergency [13]. Given these restrictions, the AC-FC technique may be most appropriately utilized when proper dynamic spacer components are unavailable or when economic circumstances make it necessary. Future studies to standardize sterilization protocol and spacer techniques with larger patient series should be performed.

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QUESTION 8: Is it necessary to revise or reduce dislocated articulating antibiotic spacers?

RECOMMENDATION: Unless the spacer is pressing against the skin with imminent necrosis/ulceration, resulting in severe, progressive loss of essential soft tissue or bone, neurovascular compromise or notable pain and disability for the patient, a dislocated or fractured antibiotic-impregnated cement spacer is safe to leave in place until definitive second-stage surgery.

LEVEL OF EVIDENCE: Consensus

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

TABLE 1. Summary of studies reporting complications of hip and knee antibiotic cement spacers in the literature

Lead Author	Year	N	Age (Y)	M/F	BMI (Kg/m2)	[1° -2° T] (D)	Follow-up (M)	Complications	Treatment
Lau	2016	72 knees	70,2 ± 1,8	45/26	32,4 ± 6,4	128,2 ± 80,8	44,9 ± 29,8		If subluxation of the articulating spacer is present, constrained revision knee systems as well as augments should be available at time of re-implantation.
Faschingbauer	2015	133 knees	70,1 ± 9,9	69/64				Fracture/fissure of the tibia (n9 - 6,8%); fracture/fissure of the femur (n3 - 2.3%); spacer fracture (n1 - 0,8%); subluxation of the patella (n1 - 0, 8%)	Not clear in the article.
Faschingbauer	2014	138 hips	69,3 ± 10, 5	Spacer fracture (n12 - 8,7%) 50% with a spacer fracture showed a stable condition. The other half underwent spacer revision. Periprosthetic femoral fracture (n1 - 0,7%) Managed Operatively Dislocation with a simultaneous spacer fracture (n1 - 0,7%) Not clear in the article				Dislocation (n12 - 8,7%)	Close reduction and stable retention in 4/12 dislocations. All other underwent spacer revision.
Jung	2009	88 hips	70	43/39		90	54	Dislocations (n15 - 17%)	12 patients >> conservatively by reduction and immobilization in a hip orthesis. The others: in one case (combined spacer dislocation and fracture) >> spacer exchange, two cases (recurrent spacer dislocations and unsuccessful conservative treatment) >> resection arthroplasty.
								Spacer fracture (n9 - 10,2%)	7 (in the distal part of the spacer stem) >> asymptomatic. The other two cases (spacer-neck fractures) >> spacer exchange.
								Periprosthetic femoral fracture (n12 - 13,6%)	4 with femoral scissure >> conservatively; 5 at 1st stage >> implantation of antibiotic-coated femoral nail and spacer implantation on top; 1 (avulsion of the minor trochanter) >> cerclage refixation; 1 fracture beneath the spacer stem >> implantation of an antibiotic-coated prosthesis stem and placement of a spacer head onto the stem.

RATIONALE

Antibiotic-impregnated cement spacers are used after resection arthroplasty, as part of a two-stage exchange procedure. The rationale for the use of spacers is to allow for delivery of local antibiotics, while managing the dead space that is left behind after resection of the components. Spacers also may facilitate subsequent joint exposure during second-stage reimplantation and, depending on their configuration, may improve function during the resection interval. Spacers can be classified as either static or articulating. There are numerous problems that can occur with the use of spacers and relative to the type of spacer used (Table 1).

Knee

In a study by Struelens et al. [1], 57% of patients experienced issues related to the use of articulating spacers in the knee. Of these, 45% were minor problems such as spacer tilting and medio-lateral translation. In their cohort, 12% of spacers had dislocated, fractured or subluxed. Possible reasons for subluxation or dislocation of spacers are inadequate soft-tissue tension and/or incorrect positioning of the spacer. In addition, pre-fabricated articulating spacers typically come in a limited number of sizes and have inadequate morphology offering minimal inherent stability. Articulating spacers rely mainly on soft-tissue tension around the joint for stability and function and soft tissues often have some compromise in this setting.

Soft tissues are not always to blame for instability associated with spacers. Even when proper tension is restored during surgery, later bone loss may cause further motion and subsidence of the spacer, leading to instability and dislocation. A study by Lau et al. [2] reported that sagittal subluxation was associated with bone defects on the tibial side. The same study found that coronal subluxation tended to be correlated with larger bone defects on the femoral side although this finding did not reach statistical significance. Lanting et al. [3] found that subluxed knees, more than one standard deviation from the mean in the sagittal plane, had lower early- to mid-term Knee Society Function Scores, but did not show any significance in other patient-reported scores like Medical Outcomes Study Short Form-12 (SF-12), Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Coronal subluxation did not affect any of these scores.

Hip

There are fewer reports related to complications of spacers in the hip. A study by Jung et al. [4] reported a total complication rate with hip spacers of 40.8% (i.e., 17% dislocations, 10.2% fractures of the spacer, 13.6% femoral fractures). These numbers were not confirmed by Faschingbauer et al. [5] who had an overall mechanical complication rate of 19.6 % (i.e., fracture of the spacer 8.7 %, dislocation 8.7 %, femoral fracture 0.7 %, protrusion into the pelvis 0.7 %, dislocation and spacer fracture 0.7 %). According to Faschingbauer et al., 50% of the patients with a spacer fracture remained asymptomatic (the spacer fracture occurred at the stem area of the spacer) and showed a stable condition, while the other half underwent spacer revision. A fracture of the proximal femur occurred in one of the study patients (0.7 %), which was managed operatively. Closed reduction and stable retention was possible in only 4 of 12 dislocations. All other patients with a spacer dislocation underwent a subsequent operation with spacer revision. There was no comparison in these studies between the functional and morbidity outcomes between the revised and the nonrevised spacers with respect to associated complications.

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5.5. TREATMENT: TWO-STAGE EXCHANGE

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QUESTION 1: What is the optimal timing for reimplantation of a two-stage exchange arthroplasty of the hip and knee?

RECOMMENDATION: The optimal timing for reimplantation of a two-stage exchange arthroplasty of the hip or knee has not been established. Reimplantation may be performed when the treating medical team feels that the infection is under control.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

There is no conclusive evidence for defining the optimal timing between resection arthroplasty and reimplantation in a two-stage revision arthroplasty for periprosthetic joint infections (PJIs). Multiple studies have reported time to reimplantation ranging from a few weeks to several months or even years [1–11]. Literature has utilized various definitions for PJI two-stage treatment success or failure as well as different variables influencing the timing of reimplantation. Due to this heterogeneity, they have failed to answer this

question. Success of treatment with a two-stage arthroplasty varies between <70 to 100%, with no direct correlation to the spacer time interval [1,2,6,7,9,11].

Several studies have reported on time to reimplantation and its influence on success or failure. Haddad et al. reported no increase inreinfection rates by reducing the interval to three weeks [5]. Sabry et al. found that an increased duration between resection and reimplantation was associated with higher rates of infection recurrence in a cohort of 314 infected total knee arthroplasties (TKAs) treated with two-stage exchange [7]. Their median interval between stages was 103 days (range, 2 to 470 days). A study by Kubista et al. [8] also found that a longer time period between spacer insertion and reimplantation was associated with increased PJI recurrence. In contrast, Babis et al. obtained a 100% success rate when using a long interval—mean 9 months (range, 8 to 12 months)—in a group of patients with a high percentage of multiresistant bacteria [9].

One common belief is that a delayed second-stage or reimplantation will result in a higher rate of treatment success. However, this is not based on strong evidence and may lead to an unnecessarily long inter-stage interval with its associated morbidity. Aali-Rezaie et al. [10], in a recent, large retrospective cohort study evaluating patients with two-stage exchange arthroplasty, did not detect a clear association between time to reimplantation and treatment failure. Furthermore, they found that delaying the time to reimplantation did not significantly improve treatment success of two-stage exchange arthroplasty. In addition, Vielgut et al. found, in a study of 76 hip infections, that patients who had their reimplantation between 4 and 11 weeks had a significantly higher success rate when compared to less than 4 and greater than 11 weeks [6].

When deciding on the optimal timing for reimplantation, most surgeons prefer to rely on a combination of clinical evaluations, such as a completely healed wound, no pain and serologic tests trending downwards after a period of antibiotic therapy [11]. Various studies recommend a complete workup with normalized laboratory and clinical variables to assure infection control prior to reimplantation.

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QUESTION 2: Is it safe to retain a stable cement mantle for later use in patients undergoing resection arthroplasty for periprosthetic joint infections (PJIs)?

RECOMMENDATION: Meticulous debridement and removal of all foreign material, including cement, should be part of resection arthroplasty in the management of PJIs. Limited data suggests that under strict conditions and following a meticulous surgical technique, a stable cement mantle in the femur may be left in place for later use in order to minimize damage to the femoral bone stock.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 63%, Disagree: 29%, Abstain: 8% (Super Majority, Weak Consensus)

RATIONALE

Historically, resection arthroplasty for PJIs involved removal of all the foreign material including cement, as these materials can act as a nidus for biofilm and persistence of infection [1–5]. However, removal of the cement mantle increases operative time and causes increased morbidity through bone loss and fractures. The in-cement revision technique is a useful, well-described technique utilized in aseptic conditions to avoid the tedious task of cement removal and therefore avoid complications associated with cement extraction [6–10]. Retention of an intact cement mantle in cases of resection arthroplasty for PJI would be preferable to avoid the morbidity associated with its removal and would make subsequent reimplantation technically easier.

The concern for retaining cement in the setting of PJI has been supported by in vitrostudies. Kendall et al. examined microbial growth of staphylococcal species on the surface of antibiotic-loaded cement discs incubated in broth. While the broth itself was sterilized by the discs after 96 hours, growth was consistently seen on the surface of the cement discs themselves. The cement, therefore, seemed to be a habitable surface for continued growth of bacteria, despite elution of antibiotics [11]. Mariconda et al. demonstrated that fluid around antibiotic-loaded cement that is sonicated can yield positive cultures, even if aspiration fluid was culture-negative, indicating that biofilms can persist on antibiotic-loaded cement [12]. Tunney et al. and Minelli et al. showed that biofilm could form even

on antibiotic-loaded cement, depending on the inoculum and the type and dosing of the antibiotic agent [13,14]. Although Griffinet al. could not demonstrate biofilm formation in explanted spacers, Ma et al. demonstrated that 30.7% of spacers had bacterial contamination at the time of the second stage [15,16]. This laboratory data should give some cause for concern for the retention of cement in the setting of infection, even if loaded with antibiotics.

The clinical data on this topic is extremely limited. There are two case series that examine this specific issue, both involving a stable cement mantle in revision total hip arthroplasty for infection. Morley et al. reviewed 15 total hips with two-stage revisions for PJIs while retaining the original cement mantle and reported infection-free outcomes in 14 of 15 patients [17]. The authors used a very strict selection criteria for the patient cohort. These selection criteria, which included a stable cement mantle, prior use of antibiotic-loaded cement and meticulous burring of the cement mantle in order to remove biofilm and liberate antibiotics were vital to the success of this technique.In a similar study, however, Leijtens et al. reported success in only 2 out of 10 patients undergoing two-stage revision total hip arthroplasty for infection at an average of 26 months [18]. It should be noted that this study did not mention whether the existing cement mantle contained antibiotics or not.

There is only one Level IV study showing good results with a retained stable cement mantle for later use in resection arthroplasty in the treatment of PJIs. While this technique presents theoretical advantages, there is a lack of robust evidence in the literature to support its routine use. Direction for further research might include the use of chemical debridement agents, such as dilute povidone-iodine, chlorhexidine irrigation and/or acetic acid preparations, which some evidence suggests might help eradicating microbes and biofilms in some settings [19]. The role of chemical debridement agents in eliminating sessile bacteria and biofilm on the surface of retained cement has yet to be explored. With further research, the answer to this question might become known.

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QUESTION 3: Should surgeons make an effort to remove cement that has extruded into the pelvis or at difficult anatomical positions in patients with periprosthetic joint infections (PJIs)?

RECOMMENDATION: The orthopaedic surgeon should carefully consider whether the potential benefits of cement extraction from the pelvis or difficult anatomical positions outweigh the potential risks of persistence of infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 85%, Disagree: 9%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Extrusion of cement during primary arthroplasty is reported to occur in 25% of patients [1]. Bacteria can form biofilm on foreign bodies in patients with PJIs [2]. Therefore, in patients with PJIs who are undergoing resection arthroplasty, it is recommended that the prosthesis and all foreign material including bone cement be removed and thorough debridement performed. Whether or not

cement in the pelvis or in difficult anatomic positions contributes to the risk of persistent infection after revision arthroplasty has not been studied.

When cement is extruded into the pelvis or difficult anatomic positions during primary arthroplasty, there is a risk of neurological (obturator nerve palsy [3,4], femoral [5] or sciatic nerve involvement [6]), urological (such as a foreign body in the bladder wall [7]) or vascular (with compression of the external iliac vein [8]) complications. During extraction of extruded cement, the risk of these complications may be even greater due to the manipulation needed for extraction.

It is common wisdom and belief among surgeons that foreign material in an infected joint may harbor biofilm formed by the infecting organism. Leaving behind foreign material during resection arthroplasty and debridement, thus, runs the theoretical risk of allowing for biofilm and infection to persist and could therefore potentially jeopardize the success of surgical debridement. The latter dogma has actually never been proven in a conclusive study. It is also known that removal of foreign material, such as cement, from anatomically sensitive and/or inaccessible areas may require a wider surgical approach (such as laparotomy for extruded cement into the pelvis) or manipulation of structures such as organs (e.g., bladder, bowel), vessels (e.g., vena cava or major veins) or nerves (e.g., sciatic or plexus). The manipulation of these structures may threaten the life of the patient and/or lead to catastrophic complications. Thus, we believe surgeons should exercise their wisdom when dealing with patients with PJIs and extruded cement or other foreign materials in anatomically sensitive and/or inaccessible areas.

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QUESTION 4: Does the use of non-antibiotic-impregnated allograft for bone defects during reimplantation increase the risk of recurrence of surgical site infections/periprosthetic joint infections (SSIs/PJIs)?

RECOMMENDATION: There is no evidence to demonstrate that using non-antibiotic impregnated allograft for management of bone defects during reimplantation (following PJIs) increases the risk of recurrence of SSIs/PJIs.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Systematic reviews were undertaken using PubMed, Cochrane Library, SCOPUS and Google Scholars databases and relevant papers were reviewed. During review, it became evident that there is a dearth of information directly assessing treatment of PJIs when a non-antibiotic-impregnated allograft was used. Overall, 51 papers were reviewed in full. The evidence is summarized below.

Following the increased popularity of the use of allograft bone in tumor surgery in the 1970s [1], infection has become a major concern. The early reports of infection rates range from 13.2% by Mankin et al. [2] to 11.7% by Lord et al. [3] and were followed by 7.9% in a comprehensive report by Mankin et al. in 2005 [4]. All authors believed that higher rates of infection could be attributed to the disease nature, extent, duration and complexity of the procedures and not related to the allograft itself [2–4].

Tomford et al., in a retrospective study, reviewed 324 patients who received allografts and showed a negligible clinical incidence of infection. The incidence related to the use of large allografts was approximately 5% in bone tumor and 4% in revision of a hip arthroplasty [5]. These rates of infection were not substantially different from those that have been reported in similar series in which sterilized prosthetic devices were used [6]. One of the early reports of allografts in revision total hip arthroplasty (THA) was published by Berry et al. [6]. They used bone allografts in 18 patients during two-stage revision of septic THA failures. At a mean of 4.2 years after reimplantation, only two patients had a recurrence of the infection (11%).

Several retrospective cohort studies have evaluated the use of allograft bone during total hip reimplantation surgery, the second-stage of planned two-stage exchange arthroplasty for infection. The majority of these studies have demonstrated recurrent infection rates of 0 - 9% in cohorts consisting of 11 -27 patients with mid- to long-term follow-up [6-12]. Two studies reported less favorable reinfection rates of 11% (18 patients, mean 4.2-year follow-up) and 14% (57 patients, mean 9-year follow-up) [13,14]. Traore et al. reported a higher rate of 20% for reinfection at mean 3 years [13]. Loty et al. reported a cohort of 90 cases with 8 (9%) reinfections over an unknown follow-up period in one-stage hip revision for infection [14].

Lange et al. performed a systematic review on using bulk allograft for second-stage re-implantation of hip arthroplasty and revealed a reinfection rate of 4 out of 43 (9.3%) at a average follow-up of 6 years. This was comparable to the reinfection rate reported for two-stage revision without using allograft [15]. Alexeeff et al. also had no recurrence of infection in 11 septic failures of THA that underwent two-stage revision THA using massive structural allografts and were followed for an average of 47.8 months [10].

Tsahakis et al. reported on 15 cases that used allograft for revision knee surgery, and of the three infected knees in their case series, there was no recurrence of infection [16]. Wilde et al. performed a retrospective review of 16 revisions total knee arthroplasties (TKAs) with allograft. There were two infected cases and neither of these experienced reinfection [17]. Stockley et al. reviewed 32 deep-frozen irradiated allografts used for the reconstruction of bone defects in 20 knees with an average follow-up of 4.2 years. Three knees developed infection (9.3%) and one of these was a revision for infection. However, they did not believe that the allograft was the source of sepsis [18].

Further reports by Harris et al. [19] (14 patients including 2 infected cases), Mow et al. [20] (15 structural allografts) and Engh et al. [21] (35 allografts) examined revision TKA cases and found no cases of reinfection [19–21]. Ghazavi et al. reported three infections (7%) using bulk allograft in 38 patients, including three infections that underwent revision. Two of the three cases who had previous infections experienced reinfection [22]. In a report by Clatworthy et al. on 52 cases, there were six infections, all of which underwent revision TKA with a bulk allograft. One of the six patients who had a previous infection developed recurrence of infection [23].

English et al. reported their results of using impaction allografting in the second stage re-implantation of 53 infected hip arthroplasties. After a mean follow-up of 53 months, four patients had recurrence of infection (7.5%) [24]. In reports by Dennis et al. (32 allografts) and Garino et al. (eight cases of impaction allografts), there were no infections at final follow-up [25,26].

Hockman et al. reviewed 65 consecutive revision TKAs including 12 infections at a minimum 5-year follow-up. Three of the 12 (25%) previously infected cases developed infections. They concluded that knees originally revised for infection were more likely to fail [27].

Bush et al. reviewed options for reconstructing massive bone loss and recommended against using allograft in some situations, including chronic infections [28]. Backstein et al. reported 68 cases of massive allografts for revision TKA and 11 of these were septic revisions. They found four infections (6.5%). The authors did not include how many of them had surgery for septic revisions. They believed that, because of the large size of the utilized allograft bone and the number of previous surgeries the patients had, the infection rate was modest [29].

Lotke et al. reported on 48 cases including one infection that received impaction allografting in revision TKA. At an average follow-up of 3.8 years, they had two infections (5%) [30]. Bezwada et al. reviewed 11 knees in 10 patients who underwent revision with distal femoral allografts and stemmed components. After a mean follow-up of 42 months they had no infections. They recommended against the use of plate fixation to decrease extensive soft tissue dissection and the risk of infection [31].

Engh et al. reported no cases of reinfection in 49 revision knees with severe tibial bone defects, five of which were revisions for infection [32]. Rudelli et al. reported on 32 loose and infected total hip arthroplasties that underwent revision with a bone graft in a one-stage procedure. After a mean follow-up of 103 months, infection recurred in two (6.2%) cases [33].

Burnett et al. reported on 28 knees that underwent revision TKA with an allograft at a follow-up of 48 months. Only one patient (3.5%), who received a cancellous graft for a contained defect, developed an infection. They did not mention if this was an infected revision [34]. Lyall et al. investigated 15 revision TKA patients, including three revisions for infections with severe tibial bone loss. These patients were followed for a mean of 5.4 years and they found one (6%) recurrence of infection at 3.5 years [35].

Bauman et al. retrospectively reviewed 74 patients (79 knees) who had revision TKAs with structural allografts. Of this cohort, 65 patients (70 knees) were followed for a minimum of 5 years or until revision or death. Five of sixteen failures were secondary to infection (7.1%). Two of these patients had a history of infection and two had local wound problems at the time of revision surgery requiring muscle flap or skin grafting. The authors concluded that the large bulk allografts were more likely to fail secondary to infection or nonunion [36].

In an overview on management of bone loss in revision TKA, Lombardi et al. did not mention infection as a disadvantage (i.e., late resorption, fracture, nonunion, or risk of disease transmission) of using an allograft [37]. Lee et al. retrospectively reviewed 27 patients who underwent two-stage revision arthroplasty using structural allografts to treat massive bone defects in infected hip arthroplasty. After a mean follow-up of 8.2 years, only one patient (3.7%) experienced a reinfection [12].

Richards et al. reported on a cohort of 24 patients reconstructed with femoral head allografts at the time of revision TKA and they compared them to 48 cases without allograft. All reported quality of life scores were higher in the allograft group. They did not observe any failures [38]. Wang et al. reported 28 patients with femoral head allografts for revision TKA at a mean follow-up of 76 months. They had no complications and no infections [39]. Vasso et al. reviewed multiple papers on options for management of bone loss in revision TKA. They concluded that modular metal and tantalum augmentation may considerably shorten operative times with a potential decrease in the incidence of complications, including infection, associated with the use of allografts [40]. In a review of 27 patients who had undergone revision TKA using a fresh frozen femoral head allograft and followed for 107 months, there was one (3.7%) recurrence of infection [41].

Recently, Beckmann et al. performed a systematic review on the treatment of revision TKA with bony structural allografts (overall including 476 cases) and porous metal cones (overall including 223 cases). They compared the failure rates using a regression model with adjustment for discrepancies in follow-up time and number of grafts used (femoral, tibial, or both). They did not separate septic revisions from aseptic revisions, but there was little difference in the infection rates between allograft and porous metal groups [42].

Mancuso et al. also reviewed the available English literature since 2007 on options for reconstruction of bone defects in revision TKA. Infection was reported in 8 of 271 (3%) allografts, 43 of 662 (6%) metal cones and 27 of 901 (3%) sleeves, indicating that the use of allografts did not lead to a higher rate of infection than metal cones or sleeves [43].

Sandiford et al. compared femoral head structural allografts and trabecular metal cones for the management of severe bone defects during revision TKA. They evaluated 30 allografts and 15 metal cones at a mean follow-up of nine years and found no differences in pain, function, or repeat revision. The reason for revision was infection in two patients. They observed no reinfection in either group, although one patient in the allograft group devel-

oped a periprosthetic fracture and developed an infection after treatment of this fracture [44].

Infection is the major cause of failure in revision TKA (44.1%) [32] and the risk is even higher in patients with septic revisions [45]. However, given the absence of any prospective controlled studies, the paucity of comparative studies with control groups and the conflicting data in case series,we could not reach any conclusion regarding the effect of using an allograft on the rate of infection in revision arthroplasty for septic failures.

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5.6. TREATMENT: SURGICAL TECHNIQUE

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QUESTION 1: Does arthroscopic surgery have any role in the treatment of acute or chronic periprosthetic joint infection (PJI) of the knee or the hip?

RECOMMENDATION: Arthroscopic surgery has no role in the treatment of acute or chronic PJI of the knee or hip.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 93%, Disagree: 6%, Abstain: 1% (Super Majority, Strong Consensus)

RATIONALE

Principles of managing PJIs include removal of infected soft tissue, bone and biofilm containing implants. Advocates of debridement and implant retention, typically for acute infection, rely on sensitive antibiotics to the causative organism and its biofilm. In open debridement, antibiotic and implant retention (DAIR), modular components are typically exchanged to improve access for thorough debridement and to reduce the biofilm volume.

Although arthroscopic surgery is attractive as a less invasive procedure than open debridement for the treatment of PJIs, it can be technically challenging to access all compartments of the joint to perform a proper debridement, risking partial surgical treatment. Partial surgical treatment risks failure to eradicate infection, side-effects from long-term antibiotic use and possible emergence of antibiotic resistance. Outcomes of staged-revision following failed partial surgical treatment are worse [1,2]. The evidence for arthroscopic washout and debridement is predominantly small, non-comparative studies [3–10]. Comparative studies of DAIR comment that successful control of infection was lower if managed arthroscopically [1].

Success is typically viewed as long-term eradication of infection off antibiotics, but function must be maintained. Poor function can be caused by infection or from pain due to loose components, inflamed soft tissues and wound-management issues caused by sinus tract formation. Aggressive surgical management involving the excision of bone, soft tissue restraints and removing well-fixed implants can challenge functional outcomes. Each individual PJI requires consideration of surgical aggressiveness to eradicate infection relative to maintaining function.

Arthroscopy in Total Knee Arthroplasty (TKA) PJI

Arthroscopic treatment of TKA PJI has variable success from 38-100%. Flood and Kolarik were the first to describe successful arthroscopic treatment of two patients with a late acutely infected TKA [3]. Waldman et al. reported that 6 of 16 patients (38%) with infected TKA who presented with less than 7 days of symptoms and who were treated with arthroscopic surgery retained their prostheses at a mean follow-up of 64 months [4]. Dixonet al. reported that 9 of 15 patients (60%) with late acute infections of TKA retained their prostheses after a mean follow-up of 50 months [5]. Chung et al. reported that 10 of 16 patients (62.5%) with late acutely infected TKA who were treated with arthroscopic surgery within 72 hours of onset of symptoms retained their prostheses at a mean follow-up of 47 months [6]. The six patients who failed arthroscopic debridement underwent successful infection eradication with open debridement with polyethylene insert exchange.

Ilahi et al. reported 5 patients with late acute TKA infections who were treated with arthroscopic surgery within 7 days of symptom onset; all patients retained their prostheses after a mean follow-up interval of 41 months [8]. Liu et al. reported on 17 patients who had late TKA infections who were treated with arthroscopic debridement combined with a close continuous irrigation-suction system; at a mean follow-up 27.5 months, 15 (88%) retained their prostheses [7].

Byren et al. [11] compared arthroscopic treament with open debridement in a retrospective review of 112 cases, 51 of which were of hips and 52 of which were of knees, to assess outcomes of patients treated for PJIs. The group found that the 15 patients with PJIs who were treated with arthroscopic washout had a significantly lower rate of success (47%) than the 97 treated with open debridement (88%) (hazard ration (HR) = 4.2, 95% confidence interval (CI), 1.5–12.5, p = 0.008). Compared to the other series, the majority of the organisms were staphylococci and 77% were early postoperative within 90 days of the implantation.

Combining these papers results in 86 infected primary TKA treated with arthroscopic debridement. In total, 54 patients (63%) were successfully treated. The success rate was affected by the infecting organism which was available in only 71 cases. The organism results were: Streptococcus 12/14 (86%), *Staphylococcus epidermidis* 11/16 (69%), *Staphylococcus aureus* 14/26 (54%), gram-negative bacilli 3/6 (50%), Mycoplasma 1/2 (50%), no growth 5/6 (83%) and polymicrobial 0/1 (0%).

The time between implantation and infection was described in 60 patients. There were eight (13%) postoperative infections using six weeks as a cut-off. Arthroscopic washout and debridement was successful in four (50%) cases. The remaining 52 cases were described as late-acute PJI with success in 36 (69%) cases.

Arthroscopy in Total Hip Arthroplasty (THA) PJI

Only two studies investigated arthroscopy in THA PJIs [9,10].In a prospective study, Hyman et al. reported eight consecutive patients who had late acute PJIs after primary THA andwere treated with arthroscopic surgery [10]. Seven infections were caused by Streptococci and one by coagulase-negative Staphylococcus. After a mean follow-up of 70 months (range, 29-104 months), there were no recurrent infections. The authors concluded that arthroscopic irrigation and debridement could benefit well-selected patients with late-acute periprosthetic hip infections.

Another study included two patients with infected THA who were successfully treated with arthroscopic debridement followed by intravenous therapy; the report did not provide additional details [9].

Arthroscopy in Chronic Late Infections

The inclusion criteria for most of the studies mention a short duration between the presentation of symptoms and time of

arthroscopic debridement and therefore there is no clear evidence exploring the role of arthroscopy in chronic late infections. The 112 PJI series treated by DAIR included 35% that were over 90 days from onset of symptoms to debridement, but this was a mixed series of predominantly open debridement with only 15 performed arthroscopically [11]. There was no sub-group analysis of the arthroscopic group available to make conclusions regarding timing or utility in treating chroniclate infections.

There is a practical role of arthroscopy as part of the management of PJIs in chronic-late infections. Arthroscopy can be part of the diagnostic workup of a painful arthroplasty allowing dynamic inspection of the components for instability and wear, ruling out non-infective causes, visualization of the synovium and obtaining multiple samples for microbiology and histology. In patients who are not well due to sepsis, particularly where delaying surgery while waiting for appropriate equipment or surgical expertise risks further health deterioration, arthroscopically obtaining microbiological samples prior to commencing antibiotics and joint washout to reduce the bacterial load can allow time for appropriate preoperative planning for definitive surgical management of the PJI.

In conclusion, the studies describing arthroscopic management of PJIs generally analyze few patients and have very specific inclusion criteria, making the data difficult to generalize. Combining the available studies, the success from acute late infection is approximately 60%. The only comparative series available concluded that arthroscopic debridement has a significantly lower success rate than open debridement. Future work could investigate specific bacterial infections that lack an ability to form a biofilm and are sensitive to long-term oral antibiotics that may be susceptible to more conservative surgical management. Overall, based on the current literature, we recommend against the routine use of arthroscopic surgery for the management of PJIs.

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QUESTION 2: Do all metallic implants need to be removed to eradicate periprosthetic joint infections (PJIs)? Does this apply to other metal hardware present (e.g., hook plates, cables) as well?

RECOMMENDATION: Complete debridement of the hip or knee joint and removal of all hardware is ideal during surgical treatment of PJIs. This principle should be followed whenever possible. However, there may be rare cases of PJIs when removal of all hardware may lead to marked morbidity and preclude future reconstruction. In the latter situation, some hardware may be retained.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 97%, Disagree: 3%, Abstain: 0% (Unanimous, Strongest Consensus)

RATIONALE

The treatment of PJIs involves the surgical removal of infected tissue and hardware in order to decrease the potential infectious bioburden. Many infecting organisms are capable of forming biofilms on foreign material surfaces. Therefore, all foreign material, including bone cement and hardware, should be removed to better treat or control PJIs.

Retained hardware prior to total knee arthroplasty (TKA) is a known risk factor for PJIs. In vitro studies demonstrate the ability of bacterial biofilms to adhere to orthopaedic implants [1–3], and the presence of extravascular foreign bodies in animal models increases the threshold for infection 100,000-fold due to a hypothesized granulocyte defect around implants [4,5]. Manrique et al. demonstrated a trend toward increasing rates of PJIs with partial or complete retention of hardware, but there was no statistical significance when compared to controls [6]. There are limited reports highlighting the need to remove hardware from around the hip or knee in the setting of PJIs. Suzuki et al. reported on their institutional experience of 2,022 TKAs. Seventeen infections were identified with a prior history of an open reduction internal fixation and the presence of retained internal fixation material was correlated with postoperative infections [7]. However, the mere presence of prior fixation material cannot fully be separated from the increased risk of PJIs in a multiply-operated joint.

While the removal of all implant materials is thought to provide the greatest benefit, the degree of tissue or implant excision necessary for infection control is currently unknown. The inability to control infection in the setting of retained hardware is often thought to be due to residual bacteria. In many cases, the morbidity of removing implants or other hardware is considered too great, and, therefore, implants are retained. Evidence for this is supported in the practice of debridement with retention of components. Partial radical debridement has proven successful in a small case series where 17 of 19 patients remained infection free with retained cemented or uncemented femoral prostheses [8,9]. In addition to the retention of metal components, there are mixed results when considering cement retention. McDonald et al. reported that 3 of 7 patients with retained polymethyl methacrylate cement had a recurrence of infection, whereas only 8 of 75 patients in which the cement had been completely removed had recurrence of an infection ($p < 0.01$) [10]. There is evidence, however, that retaining cement that would otherwise be deleterious to remove is safe and effective in the setting of infection [11].

The retention of plates, hooks or cables will often occur in the periprosthetic fracture setting. Evidence exists for successful fracture union with retained hardware in the setting of infection [12–14]. Berkes et al. demonstrated that 71% (86 of 121) successful fracture unions with operative debridement, retention of hardware and culture-specific antibiotics and suppression [12]. The retention of an intramedullary device, however, was associated with higher failure rates ($p< 0.01$). Rightmire et al. demonstrated a 68% (47 of 69 cases) success rate for hardware retention and debridement in the treatment of infected fractures [13]. When considering these results, it is important to note the clinical differences between infected fractures and infected periprosthetic fractures that communicate with the joint space, which is typically a large effective space. In postoperative spine infections, Picada et al. reported on 24 of 26 fusions healing without removal of hardware, although they achieved these results most often with secondary closure [15].

When retaining components, rifampin should be considered as part of the antibiotic regimen, particularly for staphylococcus infections. Zimmerli et al. conducted a randomized, placebo-controlled, double-blind trial and demonstrated a 12 of 12 (100%) infection control rate in the ciprofloxacin-rifampin group compared to the ciprofloxacin-placebo group (7 of 12 - 58%) when implants were retained [5]. Additionally, Trebse et al. demonstrated improved success rates with the addition of rifampin [9].

The removal of all infected material, organic or inorganic, improves the ability to control PJIs by reducing bacterial bioburden and helping to eliminate biofilm. However, the removal of these materials must be balanced with the morbidity of their removal and considered carefully in surgical planning.

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QUESTION 3: Should all knee compartments be resected during resection of an infected unicondylar knee arthroplasty (UKA)?

RECOMMENDATION: Yes, during resection of an infected UKA, other compartments of the knee, including the fat pad, should also be resected.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 80%, Disagree: 14%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

UKA has become increasingly popular among those affected by single-compartment osteoarthritis in that it preserves the integrity of the remaining knee compartments and ligaments, permitting the operated knee to be functionally and kinematically similar to the

natural knee [1]. Similar to total knee arthroplasty (TKA), periprosthetic joint infections (PJIs) after UKAs can occur with reported rates ranging from 0.2 to 3% [2,3].

There is surprisingly minimal literature regarding the treatment and outcomes of PJIs after UKA. For chronic PJIs, Labruyère et al. demonstrated 100% survivorship in a series of nine infected UKAs treated with one-stage exchange arthroplasty to a TKA at a median of 60 months, five of which were initially unsuccessfully treated with synovectomy, joint lavage and antibiotics [2]. The authors also noted that wedges (n = 6) and stems (n = 5) were required in the majority of patients. Bohm et al. performed exchange arthroplasty in two cases of PJI with one resulting in a femoral amputation [4]. One study revised two cases via a second, single-stage UKA in conjunction with synovectomy and prolonged antibiotic therapy, with the new implants being the same size as the initial implant, and with one implant being cemented with antibiotic cement, while the other case did not have a cemented implant [5]. Four studies revised nine knees to a TKA [6–9], with one study having two re-revisions following initial resection for recurrent infection [9]. Furthermore, Hamilton et al. performed three two-stage exchange arthroplasties, with one initially undergoing irrigation and debridement but ultimately requiring revision to a TKA via a two-stage exchange arthroplasty for recurrent infection [10].

Three studies successfully treated deep infection following UKA with retention of the implant with the first reporting one case treated with debridement and inlay exchange [8], the second reporting two cases treated with washout, debridement and bearing/liner change [9] and the third reporting one case treated with synovectomy and placement of gentamicin chains [11].

It is clear through the current literature that there are several viable options to treat infections following UKAs. The method that the surgeon chooses to use should be selected based on the severity and chronicity of infection as well as the amount of remaining native bone and cartilage. Bone loss is also not uncommon in the setting of infection [5]. In acute infection and in the absence of involvement of other compartments, debridement and retention may be a reasonable option. In patients with bone loss, chronic infections, or with infections that may be difficult to eradicate due to a resistant or challenging organism, a one-stage exchange or two-stage exchange arthroplasty to a UKA or TKA may be performed with the inclusion of a wedge or stem as indicated. If two-stage exchange arthroplasty is being performed, during resection arthroplasty other compartments and the fat pad should also be resected as they may harbor bacteria. This practice also allows for insertion of a proper spacer.

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QUESTION 4: Can sub-radical resection arthroplasty (leaving parts of implants in place) be considered during management of patients with chronic periprosthetic joint infections (PJIs)?

RECOMMENDATION: Sub-radical resection arthroplasty (leaving parts of implants in place) may be considered during management of patients with chronic PJIs when a component is proven to be well-fixed and its removal precludes opportunity for future reconstruction.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 68%, Disagree: 29%, Abstain: 3% (Super Majority, Weak Consensus)

RATIONALE

Two-stage revision with removal of all prostheses followed by reimplantation has been considered the gold standard to treat chronic PJIs [1–3]. However, the removal process might necessitate the use of additional procedures such as an extended trochanteric osteotomy to perform the removal of a well-fixed stem [4]. This can result in severe compromise of the proximal femur and jeopardize future fixation of a reimplanted stem. Retaining a well-fixed stem or acetabular component can be an option to avoid this in the setting of PJI treatment.

Struhl et al. [5] initially described this technique in 1989. In his case study, a 47-year-old man with a *Staphylococcus epidermidis* infection was treated by removal of the bipolar head, irrigation and debridement, retention of the femoral component and placement of antibiotic-impregnated beads. After seven weeks of intravenous antibiotic therapy, the patient underwent reimplantation of the acetabular component with an uncemented device. At 18-month follow-up, the patient had fully recovered without evidence of

infection. In 2013, Lee et al. [6] reported the results of 17 two-stage reconstructions retaining well-fixed cementless femoral stems in the treatment of PJI. At 2- to 8-year follow-up, 15 patients (88%) had no recurrence of infection and had satisfactory radiological and clinical outcomes. More recently, Ekpo et al. [7] reported on 19 patients with chronic infection whose femoral component was considered to be well-fixed and its removal would result in a marked femoral bone loss. Only two patients (11%), who additionally had failed a prior two-stage exchange, failed their secondary procedure due to recurrence of infection at a minimum of 2-year follow-up. Similar results have been published by Lombardi et al. [7] who had a series of 19 patients. At a mean follow-up of 4 years, 89% were considered to be infection-free. Two more recent publications have looked at results of this procedure with longer follow-up periods [8,9]. In a study by El-Husseiny et al. [8], 18 patients who had partial component retention were evaluated. These were carefully selected cases out of all the 293 patients who were surgically treated for PJIs at their institution. The selection criteria and indications for this approach were those who had complex total hip arthroplasties with ingrown femoral stems or complex acetabular components that were well-fixed [8]. Their reported success rate was 83%. Also, Ji et al. [9] retrospectively analyzed 31 patients. In his series patients underwent retention of components in what they called partial single-stage revision. Either the acetabular or femoral component was retained given that there was evidence of good fixation. Of the 31 patients, 27 were considered to have a good outcome (87.1%) at latest follow-up.

Results of sub-radical resection arthroplasty have shown acceptable success rates ranging from 87-89%. These can be compared to published results of two-stage results, although there is a high variability of reported success rates [10-12]. Only one study reports on one-stage sub-radical resection and retention of well-fixed components with also promising success rates of 87% [9]. We consider that a careful selection of patients with adequate evaluation of fixation is the key to determine if retention of components is a viable option. Although there is a lack of strong evidence, a partial exchange may present a better alternative than complete resection performed in two-stage revision of chronic PJIs when the stem is well-fixed with bone-ingrown stability. We therefore support the use of partial exchange in the treatment of chronic PJIs in selected cases.

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QUESTION 5: Is it possible to have an isolated infection of only a portion of the joint (for example the femur and not the acetabulum, or tibia and not the femur)?

RECOMMENDATION: Unknown. Infection of a prosthetic joint is likely to involve biofilm formation on surfaces of all foreign material. However, there may be rare circumstances when infective organisms may not be able to reach the surface of a well-fixed implant and form a biofilm.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 75%, Disagree: 19%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Using a standardized study search protocol, we performed a comprehensive review and analysis of the literature related to this subject matter. There were no specific studies examining the issue of partial infection of an implant. As a proxy, we examined the literature related to the outcome of surgical treatment of chronic periprosthetic joint infections (PJIs) when partial retention of an implant was deemed appropriate. The primary outcome measure was success of treatment at a minimum of two years, defined as infection-free retention of the implant. The search strategy and inclusion criteria were chronic PJI, total hip arthroplasty (THA), total knee arthroplasty (TKA) and partial retention. Subsequently, our search strategy yielded 9 articles for analysis, including 130 revisions (Table 1). The follow-up period was 2-8 years (mean 4.1 years) or less if failure occurred. We also recorded the types of bacteria and the success rates reported in each study.

There were no studies related to partial retention of TKA components. The overall success rates of eradication of infection ranged from 80-100% (mean 90%). There were 113 acetabulum-only revisions

TABLE 1.List of publications

Author	Year	Journal	Study Period	Country	Population Size
Faroug [1]	2009	Hip International	2004-2009	United Kingdom	2
Anagnostakos [2]	2010	Hip International	1999-2008	Germany	12
Lee [3]	2013	Acta Orthopaedica	2005-2010	South Korea	19
Ekpo[4]	2013	Clin Orthop.	2000-2011	USA	19
Lombardi [5]	2014	Bone and Joint	2011-	USA	7
Fukui [6]	2015	Journal of Orthopaedics	2009-2014	Japan	5
El-Husseiny [7]	2016	Clin Orthop.	2000-2010	United Kingdom	18
Ji [8]	2016	International Orthopaedics	2000-2013	China	31
Chen [9]	2017	International Orthopaedics	2004-2013	China	16

and 17 femur-only revisions. There were 11 failures in the acetabulum-only group (9.7%) and 2 failures in the femur-only group (11.7%). There was no statistically significant difference between the groups. The offending bacteria in the studies are similar to what is expected to be seen in PJIs.

In conclusion, given that in THA and TKA the surfaces of prosthetic material are in contact with bone and knowing the fact that infective organisms are capable of attaching to foreign material surfaces and forming biofilms, we are inclined to believe that partial infection of a prosthesis does not exist. Infective organisms are capable of accessing the effective joint space in the hip and the knee and infecting the entire prosthesis. However, there may be rare circumstances when an implant is well-fixed, either by cement or through osseointegration, and the infective agents are not able to access the prosthesis-bone interface. There were no studies to prove or disprove this assumption. If such a situation existed, then a resolute approach for radical resection of all implants could plausibly lead to an overtreatment and unnecessary morbidity.

Based on the scant data available, it appears that partial retention of well-fixed implants in patients with reconstructive challenges may be a viable option. Such surgical options should only be reserved for patients in whom removal of well-fixed implants are likely to compromise or prevent a later reconstruction. The basic principles of aggressive soft-tissue debridement and complete removal of infected implants should still be obeyed for the majority of patients.

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QUESTION 6: Should heterotopic ossification (HO) be removed during resection arthroplasty of an infected prosthetic joint?

RECOMMENDATION: We recommend that surgeons give strong consideration to removal of accessible HO in an infected prosthetic joint that will not compromise future reconstruction.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 80%, Disagree: 10%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

HO is the presence of bone in soft tissue where bone does not exist. Several risk factors have been associated with HO such as spinal cord injury, head injury, neurologic disorders, osteoarthritis, male gender, burns, other trauma with severe soft tissue damage and joint arthroplasty. The presence of HO at an infected prosthetic joint may be encountered during the time of resection arthroplasty. HO should be removed if present within the infected area, if it interferes with adequate exposure and debridement or when it could potentially interfere with function after resection arthroplasty. Following surgical resection of the heterotopic bone, beneficial effects on the range of motion and pain relief have been described. However, there are still controversies about the optimal timing for surgical resection.

A perioperative regimen is crucial for recurrent prophylaxis. Non-steroidal anti-inflammatory medications (NSAIDs) and radiotherapy have demonstrated beneficial effects on HO prophylaxis with low recurrence rates for a number of indications such as total hip arthroplasty and acetabular surgery. Resection arthroplasty is an effective modality to treat hip arthroplasty infections with HO. If subsequently the patient develops HO while he or she is mobilized, it may facilitate walking on that hip [1].

However, in an extensive search of the English literature we were unable to find any relevant studies that investigate the effect of resection of HO at the time of resection arthroplasty on surgical outcomes.

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QUESTION 7: When soft tissue coverage requires a reconstructive flap, can it be performed at the time of explant or should it be deferred until reimplantation?

RECOMMENDATION: When a soft tissue defect requires a reconstructive flap, it is safe to perform flap coverage at the time of explant or at the time of reimplantation. Early flap coverage at the time of explantation improves soft tissue biology for eradication of infection and allows for earlier mobilization following reimplantation given greater flap maturity.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

No prospective comparative studies were identified which compared patient groups who have had soft tissue reconstruction flaps performed at the time of explant versus at the time of reimplantation. Much of the literature pertinent to this question comprises heterogeneous series of patients who have exposed or infected total knee arthroplasty (TKA) implants. For TKA soft tissue defects, medial gastrocnemius rotational flaps were most commonly reported. However, many additional rotational and free flaps have been described: lateral gastrocnemius, latissimus dorsi, local fascio-cutaneous, quadriceps advancement, sartorius and rectus abdominus.

Tetreault et al. [1] published the only study identified which evaluated patients based on the timing of flap coverage. Treatment was based on surgeon opinion of insufficient soft tissues. The cohort was heterogeneous, including patients who received medial gastrocnemius flaps at the time of explantation, repeat spacer, reimplantation or irrigation and debridement with liner exchange. There was a non-significant trend toward higher failure rates when the flap was performed with spacer implantation (first or repeat) compared to definitive implants (reimplantation or retention with liner exchange). The overall reinfection rate among all groups was 52% at 4 years. Selection bias likely impacted these results and the authors clearly state that flap timing was based on necessity, rather than a belief that the timing was advantageous. Corten et al. [2] and Young et al. [3] described standardized staged protocols for the management of infected or exposed TKA implants, including soft tissue coverage at the time of explantation, with disparate results. While Corten reports 92% flap survival and one case of reinfection, patients in Young's series had a 29% amputation rate. Ries et al. [4] described a mixed cohort, which included seven patients who underwent soft tissue coverage at the time of spacer insertion. Four patients were treated successfully, while one flap failed and two went on to experience recurrent infection. Gerwin et al. [5] and Browne et al. [6] used flaps between revision stages and at the time of repeat spacer, respectively. Both series reported relative success, with 83% and 78% successful reimplantations, respectively.

McPherson et al. [7] reported on the only identified cohort of staged revision with flap during reimplantation. They described 5% recurrent infections and 33% wound complications among 21 patients.

Based on these published reports, there is limited evidence to support soft tissue flap reconstruction at the time of implant removal and antibiotic cement spacer insertion. By contrast, a small body of literature appears to support deferral of soft tissue coverage until reimplantation of a revision implant. However, these patient populations are not necessarily comparable within the limited body of evidence available. Most studies report high rates of complications, including recurrent infection, recurrent soft tissue defects and subsequent limb loss, highlighting the difficulty of this clinical problem regardless of treatment approach. Based on this literature, as well as experience, we prefer the former approach, given the benefits of improved soft tissue coverage and biology to the eradication of infection. Furthermore, performance of flap coverage at the time of explantation allows for unrestricted rehabilitation following later reimplantation.

Of note, numerous older studies were identified which describe the usage of soft tissue flaps to facilitate implant retention; however,

this approach is not considered consistent with modern, evidence-based management of exposed, infected arthroplasty implants.

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5.7. TREATMENT: PROSTHESIS FACTORS

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QUESTION 1: Does the use of cemented or cementless components at the time of reimplantation affect the success of treating chronic periprosthetic joint infections (PJIs)? If yes, what is the optimal antibiotic(s), dosage and cement to maximize antibiotic delivery and mechanical properties of the cement?

RECOMMENDATION: There is no evidence to suggest that the use of cemented or cementless components at the time of reimplantation affects the success rate of infection treatment. However, the mode of fixation may affect implant survivorship. The bone mass and the quality should dictate the choice of implant and the mode of fixation during reimplantation. If cemented prostheses are used, consideration should be given to the addition of antibiotics directed towards the infective organisms at the time of reimplantation.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

Currently, both one-stage and two-stage revisions for the treatment of hip and knee PJIs have been reported with good results [1]. Regardless of the approach utilized, the optimal method of implant fixation (cemented versus cementless) for PJI treatment success at the time of reimplantation remains unclear. When dealing with septic revisions, the surgeon is faced with two goals: infection eradication and achieving durable fixation [2]. Cement fixation has many advantages including immediate fixation regardless of bone quality, the ability to impregnate with antibiotics/antifungals and the ability to secure impaction graft or large bulk allografts [2]. The disadvantages include sclerotic or limited periarticular bone necessitating longer stems with cementation into virgin cancellous bone further from the joint in question. In the event of reinfection, removal would be technically difficult with high morbidity. The advantages of cementless fixation include the benefit of long-term biologic fixation, ease of removal in the event of acute reinfection with lower morbidity and modularity to separately address implant fixation as well as restoration of biomechanics [2]. The overall survivorship of implants in revision surgery (aseptic and septic) has historically favored cementless fixation [3-8].

However, the literature does not support one method of fixation over another with regard to infection cure rate. Furthermore, there is no data to guide choice or dose of antibiotic to be used in the cement during reimplantation. The body of literature on fixation technique used at the time of reimplantation in two-stage procedures consists of very-low quality, small, single-center retrospective studies with only half providing adequate descriptions of the reimplantation procedure and/or whether cement was used (Table 1). The definitions for successful outcomes, antibiotic management postoperatively, adjunct antibiotic delivery devices (beads, allograft, etc.) and other aspects of surgical management were heterogeneous across different studies. Similar heterogeneous data has been reported for one-stage revision as summarized in a recent systemic review by George et al. [9]. To date, there has not been a randomized controlled trial to answer this question. Overall, cementless hips appear to be the most common approach during reimplantation with good clinical outcomes (83 - 95% successful outcomes). By contrast, when described, knee reimplantation with cemented components is common with comparable outcomes (76 - 93%, Table 1), but cementless or hybrid fixation is gaining popularity [8].

Few studies have specifically investigated the presence or absence of cement use with infection cure rates. Chen et al. explored risk factors for clinical failure following two-stage total hip arthroplasty (THA) revision for infection and a multivariate analysis did not demonstrate that cementation was associated with outcomes [10]. Sánchez-Sotelo et al. retrospectively reviewed 169 hips with infected arthroplasty, all of whom had two-stage reimplantation for the treatment of an infected THA [11]. In the second stage, the femoral component was fixed with antibiotic-loaded bone cement in 121 hips; the remaining femoral components and all acetabular components were cementless. The method of femoral component fixation, either with or without cement, did not correlate with risk of

TABLE 1. Descriptive observational studies of outcomes following two-stage revision for periprosthetic joint infections (PJIs)

Author, Year	Total Cases of Two-stage Revision	Hip or Knee	Cemented or Cementless	Cure Rates
Barrack [13] 2002	12	Hip	Not described	100%
Dieckmann [14] 2014	43	Hip	Cementless	93%
Durbhakula [15] 2004	20	Hip	Not described	90%
Etienne [16] 2003	32	Hip	Not described	~90%
Chen [10] 2015	157	Hip	Cementless /hybrid/full cementation 122 (78%)/31 (20%)/4 (2%)	91.7%
Koo [17] 2001	22	Hip	Cementless	95%
Hsieh [18] 2004	122	Hip	Acetabulum 107/119, Femur 68/107 were cementless	95%
Fink [19] 2009	36	Hip	Cementless	100%
Houdek [20] 2015	57	Hip	Cementless	84%
Berend [21] 2013	189	Hip	Cementless	83%
Toulson [22] 2009	84	Hip	Hybrid 44%, cementless 43%, cemented 13%. "If a cemented prosthesis is implanted, antibiotic cement is used. The standard doses for antibiotics in implant cement are 1.2 gm of tobramycin per packet of cement, and 500 mg of vancomycin per packet of cement." Failures evenly split 3/3	95%
Fehring[2] 1999	25	Hip	Cementless."Our criteria for using cement for reimplantation are similar to those in standard revision cases. If the bone quality is such that stable fixation and bone ingrowth are unlikely, a cemented construct is recommended."	92%
Romano [23] 2012	183	Hip	Cementless. In a case-control study, outcomes are the same as per aseptic revisions (Romano 2010).	94.6%
Cabo [24] 2011	44	Knees/hips	Not described	?
Puhto[25] 2014	107	Knees/hips	Not reported	94%
Murillo [26]2008	25	Knees/hips	Not reported	100%
Bejon [27] 2010	152	Knees/hips	"Gentamicin-impregnated cement was used for cemented implants and allograft bone was used if required."	83%
Tan [28] 2016	267	Knees/hips	Not described	78%
Mittal [29] 2007	37	Knee	Resistant organisms. Cemented in all, antibiotics in 33/37; 4 reinfections.	76%
Watts [30] 2014	111	Knee	Cemented; vancomycin and gentamicin (median 1 (0-2), 1.2 (0-2.4). Comparison between obese and non-obese patients.	80% (O) 97% (NO)
Mahmud [38] 2012	253	Knee	Not described	85%
Haleem [31] 2004	96	Knee	Cemented	93.5%
Kubista [32] 2012	368	Knee	Not described	84%
Hoell [33] 2016	59	Knee	Not described	93.2%
Brimmo [34] 2016	750	Knee	Not described	83%
Cha [35] 2015	76	Knee	Cemented, 1gm vancomycin	76%
Castelli [36]2014	50	Knee	Not described	92%
Pelt [37] 2014	49	Knee	Not described	75%

infection, loosening or mechanical failure at 10-year follow-up. The authors concluded that the method of fixation used for the femoral component during two-stage reimplantation surgery should be based on the surgeon's preference for fixation combined with the assessment of femoral bone stock [11]. On the total knee arthroplasty (TKA) side, Edwards et al. found that re-revision rates for aseptic loosening were comparable with three cemented and three cementless stem constructs. The reinfection rate was also comparable between cemented and cementless stems ($p = 0.86$). Their conclusion was that cementless diaphyseal-engaging stems had a lower rate of radiographic failure than cemented stems in two-stage reimplantation. Reinfection rates remained similar despite the absence of antibiotic cement in the cementless constructs [8]. Additionally, George et al. performed a systematic review on cemented versus cementless single-stage exchange for infected THA and found no difference in infection success rates [9].

At this time, it is not clear that antibiotic-impregnated cement is required at the time of reimplantation to increase infection cure rates. Aminoglycosides and glycopeptides are known to be the two groups of antibiotics that qualify equally for incorporation into bone cement [12]. The combination of these antibiotics has the advantage of a wide antimicrobial spectrum with good elution kinetics [12]. Vancomycin is good for treating orthopaedic-related infections since Staphylococci are the most common bacteria causing such infections, and vancomycin possesses an excellent efficacy against these strains, especially resistant strains [12]. Generally, low-dose antibiotic-impregnated bone cement is defined as ≤ 4 gm antibiotic(s)/40 gm polymethylmethacrylate (PMMA) and it is used for reimplantation as higher doses affect the mechanical properties of cement [12]. If a clear benefit on infection cure rate is demonstrated by the use of antibiotic cement, further research will be required to determine the optimal antibiotic choice and dosage.

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QUESTION 2: Does the use of tantalum (Ta) augments during a single-stage revision for periprosthetic joint infection (PJI) influence the rate of surgical site infections (SSIs) or PJIs?

RECOMMENDATION: Findings of retrospective studies suggest that tantalum augments might have a protective effect against subsequent infection following single-stage revision joint in the context of PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 58%, Disagree: 31%, Abstain: 11% (Simple Majority, No Consensus)

RATIONALE

The interaction between organisms and metals used in orthopaedic surgery has been the subject of debate and investigation. Sheehan et al. [1] showed that Staphylococcal species showed greater adherence to stainless steel compared to titanium (Ti) in a rabbit model. Trabecular metal (Ta-coated) has been a popular addition to the armamentarium of the revision hip surgeon. Because of its bioactive nature and ingrowth properties, Ta is being used in primary as well as revision arthroplasty components, with good to excellent early clinical results [2-3].

It has been hypothesized that Ta might protect against infection. Schildhauer et al. [4] found that *Staphlococcus aureus* was significantly less adherent to pure Ta when compared to Ta-covered stainless steel and commercially pure Ti and Ti alloy (T1 – 6AL – 4V). However, in this study *S. epidermidis* exhibited similar adherence behavior between these metals.

Schildhauer et al. [5] also examined human leukocyte activation in the presence of Ta compared to other orthopaedic materials. They found that the extent of leukocyte activation was directly related to surface roughness. Cytokine release and phagocytic activity were both increased in the presence of Ta-conditioned media.

In a retrospective clinical study of revision total hip arthroplasty (THA) using Ta or Ti implants, 144 hips were evaluated for which revision had been performed because of infection. Failure due to a subsequent infection was 3.1% (2 of 64) in the Ta group and 17.5% (14 of 80) for the Ti group ($p = 0.006$) [6]. In a study of revision total knee arthroplasty (TKA), Ta metaphyseal cones were implanted in 21 patients (16 aseptic and 5 septic). At a mean follow-up of 36 months, only one reconstruction was removed due to persistent infection and all metaphyseal cones showed evidence of stable osteointegration [7].The results of these clinical studies also suggest that Ta might be protective against infection following revision THA and TKA.

More recently, Harrison and colleagues [8] assessed the intrinsic antibacterial properties of Ta compared to Ti acetabular components in a well-designed and controlled in vitro study. They found no difference between the two metals in terms of resistance to colonization with *S. aureus* and *S. epidermidis*.

The results of reconstruction of acetabular defects using Ta augments have been encouraging in the early and medium term. Klatte et al. [12] performed a case-control study assessing the influence of Ta augments on reinfection rates in patients who had undergone single-stage revision THA for infection. This was a retrospective case-controlled study using cohorts that were well-matched, and infection was diagnosed based on accepted, standardized criteria. There were no significant differences in the duration of surgery, blood transfusion rates or antibiotic protocols used with each group. There was no difference observed in the reinfection rates in either group (two cases in each group). Although the findings of Klatte et al. are interesting, the numbers involved were small and the presenting center has a vast experience with single-stage revision hence surgical technique as well as multidisciplinary management with a dedicated specialist microbiologist might have contributed to these results as well.

The literature certainly suggests that Ta has potentially important benefits in the reconstruction of acetabular defects. However, there is no clear evidence that acetabular augments result in a reduced incidence of infection when used in single-stage revision THAs for PJIs.

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QUESTION 3: Is the use of highly porous tantalum (Ta) associated with reduced risks of surgical site infections/periprosthetic joint infections (SSIs/PJIs) recurrences in revision total joint arthroplasties?

RECOMMENDATION: There is some evidence to suggest that the use of highly porous Ta is associated with reduced risks of SSIs/PJIs recurrences in patients undergoing revision total joint arthroplasties, particularly for treatment of PJIs.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 51%, Disagree: 36%, Abstain: 13% (Simple Majority, No Consensus)

RATIONALE

Cementless acetabular components are increasingly being used in complex revision total hip arthroplasty (THA) procedures. These implants have demonstrated favorable outcomes when compared to their cemented alternatives, with lower rates of aseptic loosening, osteolysis, fractures and infections [1]. The cementless options for revision THA procedures are components made primarily from either titanium (Ti) or Ta. Trabecular metal (TM) (Zimmer Biomet, Warsaw, Indiana, USA) constructs are increasingly utilized in difficult reconstructive procedures, especially when significant bone loss is encountered. TM is a porous composite, comprised of a carbon skeleton coated with Ta. Porous Ta coatings have a number of advantageous characteristics: increased volume of tissue ingrowth due to high porosity (75-85%); comparable elastic modulus to trabecular bone (2.5-3.9 MPa) to reduce stress shielding and favorable frictional attributes ($\mu = 0.88$) to reduce micromotion [2]. The benefits of porous metal augments are the direct ingrowth of host bone, impossibility of resorption, avoidance of disease transmission and easy availability. It has been reported in the literature that reconstruction with Ta implants can result in superior outcomes when compared to other cementless components. These results are hypothesized to be related to the superior osseointegration and have been reported both in animal and clinical practice studies [2–4].

Short- to medium-term results of porous Ta components are promising when compared to their cementless counterparts [4,5]. Flecher et al. reported global survivorship of 92.3% at 64 months with no aseptic loosening encountered [6]. Similar results have been reported by Clement et al., with implant survivorship of 92% at 5 years and no cases of radiological loosening [7]. Encouraging results have also been seen when the follow-up period is extended; Whitehouse et al. reported survivorship of 92% at 10 years for their series of patients managed with TM augments in combination with a TM acetabular component [8]. Promising results have also been reported with the use of TM cup-cage constructs, with 5- and 10-year survivorship figures of 93% and 85% respectively [9].

Wegrezyn et al. from the Mayo Clinic published their randomized control trial (RCT) comparing porous Ta ($n = 45$) with porous-coated Ti ($n = 41$) acetabular cups for primary THAs, with a minimum 10-year follow-up. Both groups had excellent overall survivorship, with 100% of patients in the TM group exhibiting osseointegration and no cup revisions for osteolysis, radiolucency or aseptic loosening. One patient (2%) in the Ti group was revised for aseptic loosening at 12 years. Radiographic analysis at final follow-up identified radiolucent lines in 4% of TM cups and 33% of Ti cups ($p < 0.0001$), raising concerns about the potential for future cup loosening and revision [10]. This concern echoed the results from the Rothman Institute, who found a significantly greater number of lucent zones in the Ti group when compared to the Ta group ($p = 0.02$), in patients reported to have major bone deficiency (Paprosky 2C, 3A and 3B) [11]. Similarly, Jafari et al. reported excellent survivorship with no differences between the two groups [11].

Klatte et al. performed a retrospective case-control study and found that the use of tantalum augmentation during one-stage exchange for infection had no effects on the incidences of reinfections or any other short-term complications. Average follow-up was only 3 years in both study groups, and the authors recommended further study to assess long term durability [12].

It has been reported that Ta, as a material, may have the ability to resist the development of infections better than Ti. A recently published retrospective case series involving 966 patients demonstrated lower rates of reinfections in cases revised for infection using Ta compared to Ti acetabular components [13]. The incidence of all-cause failures in the Ta group was lower than that for the Ti group (4.4% vs. 9.9%, $p < 0.001$). The results were more impressive in the cohort of hips revised for infection ($n = 144$). The failures due to reinfections were significantly lower in the Ta group compared to those in the Ti group (3.1% vs. 17.5%, $p = 0.006$). Three hypotheses were proposed to account for this observation:

I. Ta has a higher potential to stimulate osseointegration than Ti, and hence "dead space" is eliminated more rapidly; in addition, osteoblasts may adhere and integrate onto the surface more easily, thus depriving access to infecting organisms.

II. Due to the topographical three-dimensional structure of Ta, microbes may find it difficult to access and colonize compared to a flat surface, where a biofilm can easily be formed.

III. The chemistry or surface characteristics of Ta may be hostile to infecting organisms [13].

Adherence of bacteria to surgically used metallic implant materials is one of the most important virulence factors for local foreign body infections and a prerequisite for the development of biofilms on implants. An in vitro study from Germany tried to assess the differences between bacterial adherences to Ta vs. other commonly used orthopaedic metallic implant materials. Schildhauer et al. stated that pure Ta has a significantly lower *S. aureus* adhesion compared to Ti alloy ($p < 0.05$) [14].

An in vitro study from Sheffield et al. attempted to identify whether Ta exhibits any intrinsic antimicrobial or antibiofilm properties. Sections of both Ta and Ti were sterilized and then incubated with a low dose inoculum of either *Staphylococcus (S.) aureus,* or *S. epidermis* for 24 hours. Colony forming units (CFUs) were then quantified on Mueller-Hinton agar plates. No statistically significant differences were seen between the number of CFUs for either antimi-

crobial or antibiofilm activity in either group, thereby raising doubt regarding the latter two hypotheses stated above [15].

As the majority of reported studies are single-center with a limited study population, a large registry data approach may provide more insight. Matharu et al. reviewed the use of TM acetabular components in primary THA and compared their subsequent revision rates to non-TM coated prostheses [16]. The group performed a propensity score matched study from the National Joint Registry for England and Wales and report that five-year revision rates were significantly lower in the TM cohort compared to the control for: 1) all-cause (1.0% vs. 1.8%, $p < 0.001$), 2) aseptic acetabular loosening (0.1% vs. 0.2%, $p = 0.029$), and 3) infection (0.5% vs. 0.9%, $p = 0.001$) [16].

Laaksonen et al. report on a collaborative study by reviewing both the Australian and Swedish National Joint Registries in order to assess the risks of re-revisions between Ta and other cementless revision THAs. Included were 2,442 first-time THA revisions with porous Ta cups, and 4,401 first-time revisions with other uncemented cups. Survivorship with re-revision for any reason was comparable up to seven years between the two groups [86% (Ta) and 87% (control) ($p = 0.64$)]. Overall survivorship up to seven years with second revision for PJIs as the end-point was 97% for both groups ($p = 0.64$). Implant survival for a porous Ta cup in first-time THA revision was similar to the uncemented cup control. No benefits in survival with re-revision for infection as an end-point could be ascribed to the Ta group [17].

In summary, the results for the use of highly porous Ta components in revision THA procedures are promising with seemingly lower rates of PJIs than that for their Ti alternatives. The reasons for this reduction in infection rates are not yet known and more work needs to be done in this area.

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5.8. TREATMENT: SALVAGE

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QUESTION 1: Are there differences in outcomes and survivorship between knee arthrodesis (KA) and above-knee amputations (AKA) for chronic knee periprosthetic joint injections (PJIs)?

RECOMMENDATION: Yes, an AKA for the treatment of chronic PJI in total knee arthroplasty (TKA) has a lower functional outcome, and higher mortality rate than KA.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

One of the earliest studies on the outcomes of the salvage procedures was published in 1988 by Pring et al. They reviewed 23 patients who were treated with AKA following a failed TKA and showed that more than half of the patients were ultimately confined to a wheelchair [1]. Isiklar et al. reviewed nine AKAs that were performed after failed multiple revision surgeries for TKA in eight patients. After an average 2.5 years of follow-up, only two out of nine patients were ambulatory with walker, and one patient required wearing a prosthesis. They

believed an earlier attempt at KA with preservation of bone stock can prevent poor outcomes of AKA [2]. Sierra et al. reviewed 18,443 TKAs performed between 1970 and 2000. They found that of 67 (0.36%) patients who finally underwent AKA, 19 of them were due to uncontrollable infection. The functional outcomes of patients undergoing AKA were poor, a substantial percentage of these patients were never fitted with a prosthetic, and those who were fitted with a prosthetic seldom obtained functional independence [3].

Blom et al., in a review of 69 revision cases, found a 5.8% infection rate. Two infected cases who underwent KAs demonstrated Oxford scores comparable with patients who were treated with two-stage revisions [4]. Fedorka et al. retrospectively reviewed 35 patients who underwent AKAs after infected TKAs. After a mean follow-up of 39 months, 15 of the patients receiving AKA had died and 11 patients needed repeat surgery. Only 8 of 14 patients who received prosthetics were able to regain functional ambulation [5]. Chen et al. retrospectively studied the functional capacity of 20 cases of patients undergoing KA, and compared them to 6 previously reported cases of AKAs for PJIs after TKAs. Both physical and mental components of the Short Form-12 (SF-12) questionnaire were higher in KA group. The number of community-ambulators increased in KA group and decreased in the AKA group. They concluded that KA as treatment for recalcitrant PJIs after TKAs may have better functional outcomes compared to performing an AKA [6]. Khanna et al. found nine patients who underwent AKAs for recurrent PJIs in TKAs from 2000 to 2013. They studied their functional abilities with SF-12 and asked patients about their satisfaction through developing a questionnaire. Six of seven patients were fitted to a prosthesis and four were able to wear the device more than one hour. Despite having poor functional outcomes, all patients were satisfied with their AKA compared to their preoperative situation. They recommended considering an AKA in chronically infected prosthetic knees in patients with multiple medical comorbidities, failed multiple attempts at revisions, soft tissue compromise of the knee and excessive bone loss or severe vascular disease [7].

Rodríguez-Merchán et al. in a review of 10 papers comparing AKAs vs. KAs after failed TKAs, found that a substantial percentage of the AKA patients were never fitted with a prosthetic and those who were fitted seldom obtained functional independence. They also reported that only 50% of patients were able to walk after AKAs, while KA patients could walk at least inside the house and activity of daily living independence was achieved by majority of the arthrodesis patients. They concluded that since functional outcomes after AKA are poor and KA patients have better function and ambulatory status, KA should be strongly considered as the treatment of choice for patients who have failed treatment for infected TKA [8].

Johnson and Bannister reviewed a small series of 25 knee infections and reported that KA was the most successful treatment modality for achieving pain relief and infection control in 11 of 12 (92%) patients at final follow-up [9].

One of the rare reports on unsatisfactory outcomes of the KA was published by Rohner et al. They reported a 50% rate of persistent infection and a 73% persistent pain in 26 patients who underwent KA with intramedullary (IM) nail. All scores showed marked impairment of quality of life. They concluded that IM nailing following septic failure of revision TKA must be regarded with skepticism [10].

Carr et al. reported on patients in a national database spanning from 2005 to 2012 and found 2,634 patients with KAs and 5,001 patients who underwent AKAs for infected TKAs. They detected an increasing trend towards AKA rather than KA in patients who were older and had a greater number of comorbidities. They also found more common systemic complications, longer hospital stays, higher 90-day readmissions and more in-hospital mortalities after AKA. Arthrodesis cases, however, had significantly higher rates of postoperative infections [11].

Son et al. identified 1,182 KA and 1,864 AKA patients among a cohort of 44,466 patients who underwent revision surgery with diagnoses of infected TKA from 2005 to 2014 using The Medicare 100% National Inpatient Claims Database [12]. Their goal was to determine the frequency, risk factors associated with, and mortality of KA and AKA. They found decreasing trends toward AKAs and KAs since 2005. Clinical factors associated with arthrodesis included acute renal failure, obesity and having additional infection-related revisions. Higher Charlson comorbidity scores, obesity, deep vein thrombosis and additional revisions were factors associated with AKA, which in turn was an independent risk factor for mortality. After adjusting for age, comorbidities and other factors, mortality was higher in AKA patients. The risk of death in KA group did not change compared to patients who underwent revisions [12].

George et al. reviewed 53 cases of AKAs performed for PJIs after TKAs in order to identify the factors predicting ambulatory status after AKAs for PJIs of the knee and to elucidate the effects of this procedure on general health outcomes. After 29 months of follow-up, 43 patients were alive and 28 were available to be contacted. Fourteen patients had infection at the site of stump. A total of 47% of the patients were non-ambulatory and their functional outcomes did not improve compared to their pre-amputation status. Male gender and preoperative community ambulatory status were independent predictors of walking ability after AKA [13].

Hungerer et al. compared functional outcomes, complications and qualities of life between 81 modular KAs and 32 AKAs performed for PJIs after TKAs between 2003 and 2012, with the use of the Lower-Extremity-Functional-Score (LEFS) and the patient reported general health status (SF-12) questionnaire. After a mean interval of 55 months, recurrence of infection was higher in AKA patients (35% vs. 22%). Patients with AKAs and modular KAs showed comparable functional outcomes and qualities of life. Notably, 10 AKA patients that could be fitted with a microprocessor-controlled knee joint demonstrated significantly better functional outcomes than other amputee patients ($p < 0.01$) or modular KA patients ($p < 0.01$). The group concluded that the AKAs should be considered as an option in patients with a good physical and mental condition [14].

Wu et al. performed a systematic review of the literature and a decision analysis to determine the treatment modality likely to yield the highest quality of life for a patient after a failed two-stage reimplantation procedure of an infected TKA. Consistent evidence in the majority of case series and reviews supported that lower functional outcome and higher mortality are expected following AKA compared to KA after failed infected TKA. Based on the data, the authors concluded that KAs should be strongly considered when patients present with failed two-stage revision for infected TKA. KA is most likely to provide infection control while maximizing patient function when there is sufficient residual bone stock and when a repeat two-stage reimplantation procedure has low likelihood of success (i.e., resistant organisms, poor host and inadequate soft tissue envelope) [15].

Kohn et al. performed a review of the literature over a 10-year period. They found that KA after failed infected TKA was a difficult procedure that was associated with complications. The review revealed that bone loss of the distal femur and proximal tibia was the most important prognostic factor [16].

Additionally, in a recent article Parvizi et al. declared that complete eradication of recalcitrant PJIs can be achieved by resection of all components without reimplantation through KA or AKA. They concluded that innovations in the future such as transcutaneous prosthetic fitting may provide an improvement on what we have and allow patients with AKA to achieve functional independence [17].

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QUESTION 2: How many exchange arthroplasties are reasonable before a salvage operation (such as amputation or arthrodesis) should be considered?

RECOMMENDATION: Patients with a failed two-stage exchange arthroplasty that undergo a repeat two-stage exchange arthroplasty demonstrate poor outcomes. Failure of the repeat two-stage exchange arthroplasty appears to be dependent on the host grade and status of the extremity. Surgeons thus should consider the patient's comorbidities and expectations when deciding whether to subject the patient to repeat two-stage exchange arthroplasties. The outcomes of a third or fourth two-stage exchange arthroplasty are dismal.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 88%, Disagree: 10%, Abstain: 2% (Super Majority, Strong Consensus)

RATIONALE

Two-stage exchange arthroplasty remains the preferred method of treatment for chronic periprosthetic joint infections (PJIs) in the United States. The reported success rate of two-stage exchange arthroplasty is variable with rates ranging from approximately 70 - 90%. However, there is significant morbidity and mortality associated with undergoing multiple surgeries for management of PJIs [1,2]. Furthermore, these patients are often very fragile and poor hosts.

There are several studies in the literature demonstrating poor outcomes after the initial failed two-stage exchange arthroplasty. Kheir et al. found that in patients undergoing a second two-stage exchange arthroplasty, reimplantation occurred in only 65% of cases and successful outcomes occurred in only 61.6%. Furthermore, of the 14 cases that were not reimplanted, there was a high rate of retained spacers (n = 6), amputations (n = 5), PJI-related mortalities (n = 2), and arthrodesis (n = 1) [3]. Kalra et al. reported on a similar cohort where success was achieved in 36.4% (4/11) of patients that underwent re-revision after a prior failed two-stage exchange arthroplasty [4].

Azzam et al. demonstrated that recurrent or persistent infections after a failed two-stage exchange was found in 4 out of 18 patients (22.2%) [5]. In this series, two patients underwent a third two-stage exchange arthroplasty and both were infection-free at two years. Furthermore, Fehring et al. found that in 45 patients undergoing a second two-stage exchange arthroplasty, 22 (49%) had another revision for reinfection [6]. The latter study also evaluated the risk factors for failure and found that poor host and extremity grades were associated with an increased risk of failure. When stratified by host grade, revisions for reinfections were performed in 30% of the uncompromised hosts (type A), 48% of the medically compromised hosts (type B) and 75% of the very medically ill patients (type C). In addition, Backe et al. also investigated the outcomes of 12 patients that failed an initial two-stage exchange arthroplasty, including 9 patients treated with a repeat two-stage and 3 patients treated with an arthrodesis. While there were no instances of reinfections in either group, the three solid fusion patients were dissatisfied with their stiff limb despite its good position [6]. In patients with a failed repeat two-stage exchange arthroplasty, the organism identified is most often different than that identified in the initial two-stage exchange [6].

While the outcomes of a second two-stage exchange arthroplasty are well known, there is minimal literature regarding the expected outcomes of a third and fourth two-stage exchange arthroplasty. However, understanding the risk factors for failure after an initial two-stage exchange arthroplasty may help determine which patients are optimal candidates for additional two-stage exchange arthroplasty attempts. In patients with increased comorbidities, infection with resistant organisms, or an organism associated with

poor outcomes (e.g., fungal or enterococcus PJIs) salvage procedures should be considered.

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QUESTION 3: What are surgical alternatives to hip disarticulation in patients with persistent joint infections?

RECOMMENDATION: Surgical alternatives to hip disarticulation include resection arthroplasty when reconstruction of the joint with the use of a megaprosthesis is not possible. Hip disarticulation should be reserved for patients with systemic sepsis and/or extreme soft tissue infections of the extremity, in whom the surgery is performed as part of a life-saving procedure.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Hip disarticulation is considered a last-resort option for non-neoplastic indications including necrotizing soft tissue infections, gas gangrene and life-threatening infections [1]. Fenelon et al. [2] reported on 11 cases of hip disarticulations performed as a result of failed arthroplasties due to severe infections of soft tissues and bones, bone stock losses or vascular injuries.

The extensive loss of bone stock from failed arthroplasty procedures and revisions is a major challenge with or without infection. Fountain et al. [3] identified 14 patients who had a total femoral arthroplasty as a limb salvage procedure after complications following revision arthroplasty surgery over a 25-year period. The indications for treatment included eradication of prosthetic joint infection (PJI), treatment of infected periprosthetic fractures, massive bone loss precluding the use of stemmed prosthesis, recurrent dislocation or a combination of these factors. Six patients had no complications. Three patients developed an infection and five patients sustained repeated postoperative dislocations. Eight patients had no pain, whereas eight other patients had persistent pain necessitating prolonged opioids. There was an overall improvement in function in all patients with four patients achieving a 75% improvement.

Parvizi et al. [4] reviewed 48 patients who received a modular megaprosthesis with or without bone grafting. There were good functional outcomes in 22 patients, fair results in 10 patients and poor results in 11 patients. Three patients had died before the minimum 2-year follow-up had elapsed. They concluded that for patients with severely compromised bone stock precluding the use of conventional prostheses due to inability to achieve adequate fixation, this might be a viable salvage procedure for these patients.

Smolders et al. [5] reviewed 25 patients in a retrospective study treated with the Modular Universal Tumor and Revision System (MUTARS®); Implantcast GmbH, Buxtehude, Germany). Harris Hip Scores improved from 28 points preoperatively to 81 points postoperatively, with 24% of patients developing complications.

Berend et al. [6] reported on 59 patients that had total femoral arthroplasties for salvage of end-stage prosthetic diseases. Indications for the procedure included numerous revision total hip or knee arthroplasties, failed periprosthetic femur fractures or recurrent infections treated with multiple radical debridement surgeries. Mean follow-up was 4.8 years. The average Harris Hip Pain Score was 34 out of 44 points. Good function was achieved with 98% able to ambulate and 43% using an assistive device or cane. There were 18 complications or subsequent surgeries (30.5%). Infection occurred in eight patients and dislocations in seven patients.

Shih et al. [7] evaluated 12 patients with massive proximal femoral deficiencies who received a proximal femoral megaprosthesis for failed total hip arthroplasty (THA). They had a mean follow-up of six years. Eight (67%) patients had satisfactory results, one had a fair result and three had poor results. The complication rates were high with dislocations in five (42%), deep infections in four (33%), ectopic ossifications in one (8%), one displacement of the greater trochanter and one case of aseptic loosening. Three patients had permanent resection arthroplasty procedures for recurrent infection.

Artiaco et al. [8] reported on five patients with severe femoral bone loss and infection using a megaprosthesis in the revision of infected THA. They compared their results to four studies using megaprosthesis for a severe femoral bone loss and infection. One of the studies was inadequate for data and three were used for comparison. Their results were four out of the five patients had eradication of their infection and Harris Hip Mean Score of 74 points compared to 20 cases from three literature studies of 75 points. The literature review group had 6 (33%) patients with recurrent infections and overall complications in 8 of 20 (40%). They stated that revision with a megaprosthesis in cases of infected total hip arthroplasties with severe femoral bone loss have a high risk of complications and should be carefully evaluated and used in selected patients when other surgical procedures are not feasible.

Friesecke et al. [9] evaluated the results of total femur prostheses implanted during revision arthroplasty in 100 consecutive patients without infections. The mean duration of follow-up was five years. Sixty-five patients (68%) had no complications. Deep infection occurred in 12 patients (12%), material failure in 3 and peroneal palsy in one (1%.). The mean Enneking hip function score was 1.25 points preoperatively and improved to 3.29 points postoperatively. The mean preoperative Enneking knee score was 2.09 points and 3.29 points postoperatively. They concluded that total femur arthroplasty (TFA) is a useful implant for patients with extensive bone losses at revision arthroplasty. Although the infection rate was high, the overall functional results were rated better than good by the Enneking classification for the hip and knee.

Gebart et al. [10] reported on 45 patients undergoing revision surgeries using the MUTARS® (Implantcast GmbH, Buxtehude, Germany). The average follow-up was 39 months. Complications occurred in eight patients (18%) with one dislocation, two aseptic loosenings and five reinfections. The Harris Hip Score was 3.0 presurgical and 78 postsurgical. Castellanos et al. [11] reported on the results of 78 patients at 5-year follow-up with infected hip arthroplasties who underwent resection arthroplasty procedures. A total of 86% of patients had infections controlled and satisfactory pain relief was achieved by 83% of patients.

Ganse et al. [12] reported on 18 hips with a mean follow-up of 52 months. Thirteen hips had two-stage revisions and five patients had an excisional arthroplasties. They reported no differences in the Harris Hip Scores between the two groups, with a mean score of 60 points. Cordero-Ampuero et al. [13] reviewed the results of resection arthroplasty procedures in the literature concluding that there was wide variability in satisfaction ranging from 13-83%. Resolution of infection occurred in anywhere from 80-100% of patients. Risk factors for failure included rheumatoid arthritis, methicillin-resistant *Staphylococcus aureus* (MRSA) and enterococcal infections and retention of cement. Pain was reported as severe in 16-33% of patients, moderate in 24 - 53%, and mild in 76%. Twenty-nine percent were able to walk independently, and 45% of geriatric patients were unable to walk. Harris Hip Scores ranged from 25 to 64 points.

Korim et al. [14], in a systemic review of proximal femoral arthroplasty (PFA) for non-neoplastic conditions, reported on 14 studies with an average of follow-up of 4 years (range 0-14 years) describing 356 PFAs. Complications most commonly occurring were dislocation (15.7%) and infection (7.6%). The mortality rate ranged from 0 to 40%.

In conclusion, several alternatives to hip disarticulation exist, including the resection arthroplasty and the implantation of megaprosthesis such as proximal and total femoral arthroplasties with or without allograft. However, the efficacy and indications of these procedures remains unclear due to low-level evidence and short-term follow-up. Further higher-level studies are required to better guide treatment in these complex clinical settings.

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5.9. TREATMENT: ANTIMICROBIALS

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QUESTION 1: What is the recommended duration of antibiotics after a single-stage exchange for periprosthetic joint infections (PJIs)?

RECOMMENDATION: In the setting of single-stage exchange arthroplasty, intravenous antibiotics should be administered for 10-14 days followed by oral antibiotics. Generally, the overall duration of antibiotics of 4-6 weeks is sufficient.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 73%, Disagree: 23%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

The two-stage exchange arthroplasty is the preferred method for treatment of chronic PJIs. However, the single-stage exchange procedure has been gaining popularity, demonstrates comparable outcomes regarding infection control and offers various benefits for

patients compared to two-stage exchange [1–3]. Unfortunately, there are limited studies examining the issues of antibiotic administration following one-stage exchange arthroplasty. In addition, the duration of antibiotic treatment after two-stage exchange arthroplasty is not well determined either.

Most studies related to one-stage exchange arthroplasty highlight the importance of preoperative identification of the infective organism [4–11]. This is important for numerous reasons, including the ability to add the appropriate antibiotics to polymethyl methacrylate cement during reimplantation as well as administering the appropriate antibiotics after the procedure. Antibiotic therapy following single-stage revision surgery usually starts with an intravenous agent based on the antibiogram of the infective agent. Intravenous antibiotics are usually administered for a few days and then replaced by oral agents if available. In the postoperative period, antibiotics are adjusted to the susceptibility reports from intraoperative samples. In a Similar fashion to two-stage exchange arthroplasty, antibiotics are selected in accordance with organisms and sensitivities and are subsequently continued for four to six weeks [6,10,12–14].

Some authors continued the antibiotic therapy until inflammatory markers (C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR)) as well as nutritional markers, such as plasma albumin concentration, return to stable limits (levels normalized in 90% of cases) [10]. Normal levels for serological markers are thought to be an ESR of 30 mm/hour, CRP of 10 mg/L, and albumin of 35 to 50 gm/L.

Other investigators believe that the type, course and duration of antibiotic treatments for patients undergoing one-stage exchange arthroplasty needs to be determined by a designated infectious disease consultant [4]. In this study, the average duration of the antibiotic treatment was 14 days (range, 10-17 days). Duration was determined by wound healing and laboratory infection parameters. No prolonged oral antibiotic therapy was administered in all 70 cases.

The importance of the local delivery of antibiotics during one-stage exchange arthroplasty has not been well studied. Some surgeons, including those at the HELIOS ENDO-Klinik, believe that the addition of antibiotics to cement during reimplantation plays a major role in infection control. There are two studies that point to the potential importance of antibiotics in cement [12,15]. In the latter study, the infection free rate was under 60% for patients undergoing one-stage exchange arthroplasty. Culture-specific antibiotics were given for at least six weeks to all the patients, but the single-stage exchange arthroplasty was performed with cementless total hip arthroplasty without local antibiotics. It is important to mention that the findings of low infection control could relate to other factors (e.g., how the surgery was performed) and may not be related to local antibiotic delivery at all.

Despite the paucity of concrete evidence with no randomized clinical trials available on the subject of antibiotic treatment after one-stage exchange arthroplasty, the use of antibiotic therapy following single-stage revision procedure is a universal practice. However, there is a lack of evidence for the duration of therapy. Currently, the orthopaedic community feels that a few weeks of antibiotic treatment, following one- or two-stage exchange arthroplasty is needed. Whether this will stand the test of time remains to be seen. In the absence of evidence to the contrary, we believe that patients undergoing one-stage exchange arthroplasty for the management of PJIs should receive four to six weeks of antibiotic treatment, which can be started as intravenous for a few days and switched to oral antibiotics soon after. We also feel that the dose, duration and type of antibiotic therapy should be individualized for most patients based on numerous metrics that influence the outcomes of treatment of PJIs, including the host type, organism virulence, the complexity of the procedure and soft tissue status.

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QUESTION 2: Are there any tests that can guide antimicrobial treatment in patients with periprostetic joint infections (PJIs) so as to determine when treatment may be discontinued?

RECOMMENDATION: No. There are no tests that can be used to guide therapies and monitor responses to treatments in patients with PJIs. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are considered useful for monitoring responses to treatments; however, sustained elevations after treatment does not predict persistent infections. Emerging biomarkers, such as D-dimer and presepsin, have shown promising results. Nevertheless, more studies are required to assess their role in monitoring response to treatment in patients with PJIs.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

The diagnosis of PJIs remains a challenge. Currently ESR and CRP are the most commonly used serological markers used for diagnosis. More recently, serum molecular biomarkers such as D-dimer and presepsin have emerged as potential diagnostic tools. However, determining whether the infection is controlled after surgical and antimicrobial treatment is even more difficult. There are limited studies assessing the roles of biomarkers in the follow-up periods of these patients; most of these studies have focused on diagnostic performance. No studies were found to specifically assess the role of biomarkers for guiding the antibiotic treatment protocols. However, there are studies that evaluate the roles of these markers in determining reimplantation timing and prognosis of PJIs.

Of the 11 published studies that were found to be relevant to this topic, 9 were prospective nonrandomized trials that focused on comparing the levels of biomarkers at the time of the diagnosis and reimplantation. These studies have shown that serum ESR and CRP are poor predictors of persistent infections and that they are frequently abnormal even when the infection has been controlled. New markers, such as the cytokines in synovial fluid, leukocyte esterase and serum D-dimer, tend to normalize at the time of reimplantation. However, more studies are required to show their trends with antimicrobial treatments.

Sanzén et al. studied the performance of serum ESR in 76 patients with PJI and found that in treated infections, ESR decreased to a lower value compared to the initial assessment [1]. In those with persistent infections there was a non-significant increase in ESR after 6 weeks, 3 months, 6 months and 12 months; the average ESR was above 30 mm/hr; and in resolved cases ESR was lower than 20 mm/hr. However, the authors did not take into account patients who had inflammatory diseases. Likewise, George et al. evaluated the values of ESR and CRP in 14 infected arthroplasties in patients with inflammatory arthritis, finding that these markers remained elevated in the infected group [2]. Shukla et al., Ghanem et al., Tornero et al., Hoell et al. and Kusuma et al., all showed that ESR and CRP remained elevated in more than one-third of cases in which the infection was eradicated, demonstrating that ESR and CRP often fail to normalize and do not reflect infection eradication [3–7].

Frangiamore et al. evaluated cytokine profiles of the synovial fluid between the first and second stage of a two-stage exchange protocol for PJIs in order to determine the cytokines that can indicate resolved infections [8]. The reimplantation (second-stage revision) was performed after symptom resolution, completion of antibiotic treatment (3-16 weeks, mean of 6 weeks), and normalization of CRP and ESR in addition to negative cultures by aspiration. Interleukin (IL)-1β and IL-6 had the best performance for determination of infection eradication.

Kheir et al. assessed the leukocyte esterase (LE) strip test for its ability to predict persistent infections in patients with PJIs [9]. Patients were evaluated at the time of reimplantation with the LE strip test, considering 2+ as a positive read. The LE test was negative in all reimplantations that did not fail. The authors found higher failure rates in those who had positive test results at the time of reimplantation.

A single prospective multicenter study by Marazzi et al. evaluated the trends of presepsin and chemokine (C-C motif) ligand 2 (CCL2) in 30 patients with PJIs [10]. The authors found a gradual decrease in the first week after surgery and reach values similar to the control group (patients without PJIs) in the first month and three months after the first revision. Another prospective study conducted by Shahi et al. evaluated the utility of D-dimer in the diagnosis of PJIs and also examined its role in determining the timing of reimplantation [11]. The authors found that serum D-dimer levels fell below the diagnostic threshold at the time of reimplantation in resolved cases. Furthermore, serum D-dimer was able to indicate the persistence of infection at the reimplantation time if the values were greater than 850 ng/mL (the recommended cutoff). Whether serum D-dimer levels can guide antibiotic treatment and have a consistent trend in response to antibiotics remains to be evaluated.

In conclusion, there is no single test or a gold standard that can indicate infection eradication in patients with PJIs. Although there are several studies on biomarkers for diagnosis, studies on responses to antibiotic treatments in patients with PJIs are lacking.

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QUESTION 3: Does the International Consensus Group (ICG) agree with the Infectious Diseases Society of America (IDSA) guidelines regarding the recommended duration of antibiotic therapy in orthopaedic infection?

RECOMMENDATION: There is some disagreement between what the ICG and the IDSA recommends regarding the duration of antibiotic treatments for different infective organisms. The differences between the two organizations resides on the duration of oral antibiotic therapy following a pathogen-specific intravenous (IV) antimicrobial therapy.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 82%, Disagree: 3%, Abstain: 15% (Super Majority, Strong Consensus)

RATIONALE

The optimal length of antibiotic treatment following surgical treatment of periprosthetic joint infections (PJIs) by resection arthroplasty, one-stage exchange arthroplasty, or debridement and implant retention remains unknown. There are numerous studies related to this subject and during the last meeting of the ICG, it was felt that antibiotic treatments between two and six weeks appeared to be sufficient for patients with PJIs.

The last ICG found no conclusive evidence regarding the ideal duration of antibiotic therapy when considering treatment following resection arthroplasty due to PJIs. They found that the ideal duration of antibiotic therapy, either IV or combined with oral medications, was unknown. Cost and resistance were lower when decreasing the time of antibiotic regimens [1–6]. Most of the literature, at the time, recommended antibiotic therapy between 6 and 12 weeks, although Bernard et al. found that 1 week of an IV antibiotic regimen plus a following 5 weeks with oral regimen was sufficient to control infection. This study involved irrigation and debridement (I&D), single-stage exchange arthroplasty and two-stage exchange arthroplasties [4]. Stockley et al. used a short two weeks IV-only antibiotic therapy following I&D and placement of an antibiotic-impregnated cement spacer, and noted an 87% success rate [7]. Nevertheless, the ICG strongly recommends a course of two to six weeks of antibiotics.

The ICG then explored how the duration of antibiotic treatments could be determined, agreeing that there was not enough evidence to determine whether biomarkers or clinical symptoms could be used to monitor response to treatment.

Additionally, the ICG attempted to determine the duration for antifungal therapy in the presence of fungal PJIs. They strongly agreed upon consensus stated that systemic antifungal treatment should be initiated before resection, and continued for at least six weeks, and stopped before reimplantation, without a need (in most cases) to restart antifungal therapy. For Fluconazole, the literature had 3 to 6 weeks or more (in some studies even 26 weeks) before reimplantation, then no further treatment, or only 2 to 6 weeks more after reimplantation. For Amphotericin B, the duration was often found to be about six weeks before reimplantation [8–20].

IDSA Guidelines

The IDSA guidelines suggest no more than a 6-week course of antimicrobial therapy following resection arthroplasty for PJIs due to more virulent organisms such as *Staphylococcus aureus* [21].The IDSA recommends two to six weeks of pathogen-specific IV antimicrobial therapy combined with 300 to 450 mg of rifampin given orally twice daily. The treatment should continue with rifampin plus a companion oral drug (ciprofloxacin (A-I), or levofloxacin (A-II), or others for a total of three months for Staphylococcal total hip arthroplasty PJI, treated with one-stage exchange or with debridement and retention of the prosthesis. The IDSA recommendation for Staphylococcal total knee arthroplasty PJI is the same, but for a total of six months when treated with debridement and prosthesis retention.

For organisms other than Staphylococci, the IDSA guidelines recommends an initial course of pathogen-specific IV therapy for four to six weeks, or highly bioavailable oral antimicrobial therapy (B-II). Chronic suppression after fluoroquinolone treatment of gram-negative bacilli was not unanimously recommended [21]. Longer courses of combination antimicrobial therapies of six months or more are recommended by the current guidelines and reports for bone infections due to rapidly growing mycobacteria (RGM) [22,23].

IDSA guidelines recommend a minimum of six weeks of antifungal therapy for fungal PJIs, but a longer course of antifungal therapy has been considered to be an essential factor for the success of fungal PJIs treated with staged reimplantation. Phelan et al. administered antifungal therapies after resection arthroplasty for six weeks to nine months in four patients who underwent two-stage reimplantations [8].

Regarding the IDSA guidelines on the treatment of osteomyelitis due to invasive Candidiasis, they recommend treatment duration from 6 to 12 months.

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QUESTION 4: Is the type, dose, route of administration and duration of antimicrobial treatment influenced by the type of infective organism causing periprosthetic joint infection (PJI)?

RECOMMENDATION: The duration, dose, route of administration and the type of antibiotic administered to patients with PJI is determined by the type of infective organism(s) isolated.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

There have been reports showing increased risks of treatment failure reported in patients with a sinus tract [1] and infections due to certain organisms such as *Staphylococcus aureus* [2], methicillin-resistant *Staphylococcus aureus* (MRSA) and gram-negative organisms [3–11] when not treated with a rifampin combination. For Staphylococcal PJIs, the Infectious Diseases Society of America (IDSA) guidelines recommend, based on expert opinion, two to six weeks of pathogen-specific intravenous (IV) antimicrobial therapy in combination with rifampin, followed by rifampin plus a companion oral drug for a total of three months [12].

The duration of antimicrobial therapy for most bacterial PJIs depends on the type of surgical procedure used to treat PJIs (debridement and retention vs. one-stage, vs. two-stage exchange, etc.) rather than the infecting microorganism itself.

One retrospective cohort study of 39 patients with PJIs undergoing single-stage exchange, of which 28 had Staphylococcal infections, demonstrated that two weeks of intravenous therapy followed by three months of oral antimicrobial therapy was sufficient to control the infection [13]. This study was limited by its small cohort size, lack of a control group and possible confounding variables.

The optimal duration of antimicrobial therapies in two-stage exchange arthroplasty is unclear. Multiple cohort studies have demonstrated acceptable cure rates in two-stage exchange arthroplasty with the use of six weeks to three months of total antibiotic therapy (IV and oral antibiotics) [14–19].

These retrospective cohort studies included a variety of infecting organisms, including *Staphylococcal* PJIs. These studies did not report any robust evidence that outcomes were worse for any organisms. There are no prospective trials directly comparing the duration of antibiotic therapy for Staphylococcal PJIs managed with two-stage exchange arthroplasty.

A retrospective cohort analysis of 30 patients with Streptococcal PJIs demonstrated high failure rates of 45%, in patients who underwent two-stage revisions [20]. The patients were managed with 2 weeks of IV antibiotics followed by 10 weeks of oral antibiotics.

Streptococcal infections are generally thought to be very responsive to treatment due to their broad antimicrobial sensitivity, including penicillins and cephalosporins. However, the high failure rate in this single-center study has not been further studied in other trials.

In the series reported by Eid at al., six of the eight patients with rapidly growing mycobacteria (RGM) PJIs received ≥ 1 active antimicrobial agent for at least six months [21]. In this series, the duration of effective therapy was as short as 16 weeks and as long as 55 weeks after resection arthroplasty, but other cases from other series were treated for as short as 3 weeks to as long as 112 weeks [22–28]. However, the optimal duration of antimicrobial therapy for RGM PJIs remains unknown. Shorter courses of three months for total knee arthroplasty (TKA) PJI, and two months for total hip arthroplasty (THA) PJI treated with debridement and retention of the prosthesis have been successful in 87.5% of the patients treated when compared to 89.5% of the patients in the same cohort treated with six months and three months respectively [29].

Rare cases of *Mycobacterium tuberculosis* and *Mycobacterium kansasii* PJIs required long courses of antimycobacterial therapies of 12-18 months [30,31]. The optimal medical and surgical therapies for *Mycobacterium tuberculosis* PJIs are unknown. Initial therapy should include isoniazid, rifampin and pyrazinamide, with the addition of ethambutol or streptomycin in case of suspected isoniazid resistance [32]. Management was successful in patients with unsuspected *Mycobacterium tuberculosis* PJIs incidentally discovered at the time of implantation or in the early postoperative period with non-rifampin anti-tuberculous combination therapies for 12-18 months [33,34].

Many authors favor a total of six months of antifungal therapy (fluconazole) that may start after resection arthroplasty and continue until after reimplantation, but a definitive duration of therapy has not yet been established [35–37].

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QUESTION 5: When a patient undergoes aseptic revision and intraoperative culture(s) grow an organism, should patients be treated with antibiotic therapy?

RECOMMENDATION: Antibiotic therapies are recommended if two or more cultures isolate the same organism, as per the MusculoSkeletal Infection Society (MSIS) and the International Consensus Group (ICG) criteria for prosthetic joint infections (PJIs). Antibiotic therapies may not be required when a single intraoperative culture isolates an organism. However, there may be circumstances when a single positive culture, combined with other tests, may indicate the presence of an infection and treatment would be indicated.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

It is important to evaluate patients undergoing revision arthroplasty for evidence of infection. Most of these evaluations are performed preoperatively. Revision surgery is then performed when the patient appears to be clear of an infection. The incidence of positive operative cultures in this setting varies extensively from 0-44% and the significance of these positive cultures is often uncertain [1-3]. Studies of the clinical outcomes of patients with positive cultures at revision surgery have been mainly retrospective and have limited and inconsistent conclusions [3-10].

If two or more operative cultures grow the same microbe, then treatment for PJI would be appropriate, as per the MSIS and the ICG criteria for the diagnosis of PJI [11,12]. However, if only one operative culture has bacterial growth, then the likelihood of a culture contaminant increases. An old but valuable study by Atkins et al. in the microbiology literature can be helpful in this analysis [13]. This prospective study found that when three or more operative cultures are obtained, a single positive culture reflected PJI due to that organism 13.3% of the time; two positive cultures were indicative of PJI in 20.4% of patients and three or more cultures positive for the same organism signified a PJI in 94.8% of patients. Based on this data, the risk of treating a patient with a substantial course of antibiotic therapy may well out-weigh the benefit if a single positive culture is associated with PJI in only 13.3% of cases. Patients in this category can be observed without antibiotic therapy, with an appropriately-timed, postoperative arthroplasty aspirate culture to help determine if the operative bacterial isolate is a contaminant rather than a true pathogen.

Other issues in the present literature which limit us in making solid conclusions include:

1. Lack of standardization of operative culture specimens to be submissions of tissues or fluids, but not swabs.
2. Need to analyze operative culture positivity occurrences with knowledge of the duration of the surgery. Revision arthroplasty surgery is usually of longer duration than primary implantation and intraoperative culture-positivity may only be a surrogate marker for the duration of the surgery, particularly if the operative cultures are obtained toward the end of the surgery.
3. A single operative culture which grows an organism, which was the pathogen treated for a patient's prior PJI, needs to be analyzed separately from those which grow a microbe that is unrelated to any previous infection. Further analysis may find that, whereas growth of a prior known pathogen represents persistence of true infection, growth of a single, entirely different organism is likely to be a contaminant.
4. Although difficult to perform, prospective, controlled studies are much more likely to result in solid conclusions than retrospective analyses.

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QUESTION 6: When should rifampin be added to the regimen of antibiotics for management of patients with periprosthetic joint infections (PJIs) undergoing surgical treatment?

RECOMMENDATION: Rifampin should be considered in the treatment of staphylococcal PJIs in patients managed surgically with debridement, antibiotics and implant retention (DAIR) or single-stage exchange where activity against biofilm is required. Rifampin should only be used in combination therapies, with the best reported combination appearing to be with a fluoroquinolone.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

The excellent efficacy of rifampin against biofilm produced by staphylococci has been shown in vitro, in animal models and in patients with orthopaedic implant-related infections undergoing DAIR [1–8]. Nevertheless, rifampin should be used with care because of the danger of rapid emergence of resistance and potential unwanted effects, such as severe nausea, hepatotoxicity, interstitial nephritis and cytopenia [9,10]. Rifampin is a potent inducer of the cytochrome P450 oxidative pathway and can result in significant drug interactions [10,11]. Monotherapy is known to quickly promote rifampin resistance and must therefore be avoided [12,13]. The emergence of rifampin resistance in *S. aureus* is of particular concern [8,14]. The best documented combination partners for rifampin are fluoroquinolones [15,16].

Clinical data supporting the use of combination rifampin antimicrobial therapy and surgical debridement for the treatment of staphylococcal PJIs are available [14,17]. Widmer et al. showed in an open-label study that 9 of 11 patients (82%) with staphylococcal or streptococcal PJIs that could not undergo removal of hardware were successfully treated with rifampin in combination with either a beta-lactam or with ciprofloxacin [1]. A randomized controlled study by Zimmerli et al. showed that among 24 patients with methicillin-susceptible *Staphylococcus aureus* (MSSA), or coagulase-negative staphylococcus (CNS)-PJI, with stable implants and a short duration of infection managed with DAIR. Those able to tolerate long-term (three to six months) combination therapy with ciprofloxacin-rifampin achieved cure at higher rates than those treated with a ciprofloxacin-placebo [15].

Trebse et al. followed 24 patients with PJIs and retained implants prospectively over 4 years, showing 83% with a successful outcome. A total of 17 of the patients had Staphylococcal infections, and were treated with rifampin combination therapy; two of the four patients who failed had staphylococcal infections, one with methicillin-resistant *Staphylococcus aureus* (MRSA) and one with CNS [17].

Retrospective case series have described the success of rifampin combination therapy [10,14]. Successful treatments with rifampin-fluoroquinolone therapy was shown by Berdal et al. and Barberan et al. [19,20]. Rifampin, in combination with other antibiotics, including fusidic acid, vancomycin or daptomycin, has also been reported to be effective [21-23]. Many of the reported case series primarily address the successful treatments of MSSA and CNS infections. Barberan et al. observed a non-significantly ($p = 0.08$) higher failure rate in 7 MRSA-infected, as compared to 14 MSSA-infected patients. More important, in patients with a duration of infection ≤ 1 month treated with levofloxacin plus rifampin, the outcome was significantly better than that for patients with a longer duration of infection [24]. A cohort study by Peel et al. included 43 methicillin-resistant Staphylococcal infections (24 MRSA) and found 86% of patients were treated successfully, most with rifampin-fusidic acid. The found eight out of nine failures were in MRSA cases [25]. A retrospective multicenter study by Lora-Tamayo et al. reported on 345 *S. aureus* PJIs managed with joint retention, including 81 MRSA cases. A total of 88% of patients received rifampin combination therapy and failure rates were similar in MRSA (46%) and MSSA (44%) cases [26].

The Infectious Diseases Society of America (IDSA) PJI and MRSA management guidelines recommend the use of rifampin combination therapy (2-6 weeks of pathogen specific IV antimicrobial therapy plus rifampin followed by 3-6 months of rifampin plus an oral companion drug) in the treatment of staphylococcal PJIs/hardware infections in patients managed with debridement or single-stage exchange [27,28]. European guidelines include similar recommendations [29].

Unanswered questions regarding the role of rifampin remain; however, many clinical studies have focused on rifampin-quinolone combinations, with little information available for beta lactam-rifampin therapy. Of note, fluoroquinolone-resistant Staphylococci are found in many settings, especially in MRSA-strains [30]. The emergence of rifampin resistance can occur even when using combination therapies [8,25,26,31]. Drug interactions lowering the serum concentrations of companion antimicrobials, including fusidic acid and clindamycin, have been reported [32,33]. The clinical significance of these interactions, however, is still unknown. Additionally, the optimal duration of combination antimicrobial therapies, including rifampin, for the treatment of prosthetic joint infections with retained hardware is not yet known. While extended treatment (3-6 months) is recommended and often used, shorter treatment courses may be as effective in some settings [34].

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QUESTION 7: What is the optimal antibiotic therapy in cases of culture-negative (CN) periprosthetic joint infections (PJIs)?

RECOMMENDATION: In patients with true CN PJIs, the antibiotics should be selected to have broad spectrum activity against both gram-positive and gram-negative organisms. In addition, the exact choice should relate to the known modern epidemiology in that country.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 87%, Disagree: 6%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

In the literature, rates of CN PJIs vary from 0-42% but reports suggest that the outcomes are not necessarily worse than for culture positive cases if rigorous and robust pathways for diagnosis and management are followed [1–7]. Factors associated with increased risk of culture negativity include prior antibiotic use, delay in transportation of the samples to the laboratory and variations in culture techniques, including short duration of culture [1,8–11]. It is important to note that several studies demonstrate that administration of antibiotic prophylaxis prior to obtaining culture samples did not interfere with isolation of the infecting organism [12].

A recent systematic review by Yoon et al. evaluated clinical studies related to culture-negative PJI. After exclusions, seven studies were included in the analysis, with all studies being retrospective [1,4,6–8,12–15]. Of these, four studies defined PJI using MusculoSkel-

etal Infection Society (MSIS) criteria [6,13–15]. In the majority of these studies glycopeptides, such as vancomycin, were used followed by cephalosporins, beta-lactams, quinolones or combination therapy. The duration of intravenous antibiotics for CN PJI was usually six weeks. The investigators also noted that the use of antibiotics for CN PJI was accompanied with appropriate surgery, stating that the choice of surgical strategy greatly affects the treatment results of PJI. Most of the included studies reported that two-stage arthroplasty followed by 4-6 weeks of antibiotic therapy was effective with a success rate of 70-100%. Six of the seven studies in this review demonstrated similar success rates between culture-positive (CP) and CN PJI, with one reporting greater success for CN PJI [1,4,6–8,13–15]. The authors of the systematic review recommended that further studies are required to determine optimal therapy for patients with CN PJI. The latter systematic review did not include studies that have demonstrated a suboptimal outcome for patients with CN PJI [16–18].

A few recent studies have attempted to further explore the issue of CN PJI. Kang et al. reported on the challenges of selecting the appropriate antibiotics and the treatment of CN PJI was commenced with cefazolin and changed to glycopeptides if infection did not respond to the initial treatment [18]. Wang et al. also reported on the challenges of treatment for CN PJI [17]. They utilized intravenous vancomycin and/or an aminoglycoside for two weeks followed by an oral antibiotic such as levofloxacin and rifampin for an additional four weeks. A cement spacer containing vancomycin/meropenem was used in their cohort. In another study Peel et al. reported the use of vancomycin and cephalosporin followed by a broad spectrum oral combination comprising fusidic acid, rifampin +/- ciprofloxacin for a median of 7 months (3-20 months interquartile range) in the majority of the patients but choice of regimen varied by presentation [9].

In 2013 Marschall et al. published a survey in which members of the Emerging Infections Network were asked about current treatment of PJI. Regarding CN PJI, the vast majority of the responders chose a two-drug regimen in hip and knee infections, most commonly using vancomycin with ceftriaxone or vancomycin with oral fluoroquinolone as upfront antibiotic treatment [19].

In summary, it appears that the rate of CN PJI varies vastly from one study to another, perhaps reflecting the variability in definition of PJI, differences in culture techniques and the local epidemiology. Despite the presence of some studies demonstrating acceptable outcomes for CN PJI, the selection of optimal antibiotics for these cases remains challenging. The majority of reported series utilize a combination of antibiotics in the CN PJI. In an effort to reduce financial and psychological costs associated with optimal management of CN PJI, all efforts should be made to isolate the infecting organism. Similar to culture-negative endocarditis, zoonotic agents such as *Coxiella, Brucella, Bartonella* and *T. whipplei* are not easily detectable by the usual means and are not treated by common empirical agents such as glycopeptides [20]. A recent study has demonstrated that next generation sequencing (NGS) has a promising role in isolating the infecting organism in up to 90% of CN PJI cases [21]. Based on the emerging data, consideration should be given to the use of NGS or other molecular techniques in isolating of the infecting organism in patients with CN PJI. Serologies or serologic markers for certain zoonotic and endemic fungal infections should also be considered in the appropriate context.

If all attempts to isolate the infecting organism fail, then strategies employed in choosing an antibiotic regimen for CN PJI must be individualized based on risk factors, previous history and knowledge of the local epidemiology. The antibiotic treatment of CN PJI usually includes broad spectrum antibiotics with a prolonged intravenous phase. Glycopeptides play a pivotal role but consideration should be given to the use of multiple-drug regimens.

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QUESTION 8: What antibiotic therapy and duration of treatment should be used in Enterococcal periprosthetic joint infections (PJIs)?

RECOMMENDATION: Based on the limited available evidence, combination antimicrobial therapy should be considered for the treatment of Enterococcal PJIs, at least during the first weeks of treatment. Antibiotics should be tailored according to the susceptibility of the infective microorganism.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 85%, Disagree: 9%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Enterococci are often part of polymicrobial infections [1,2], have the ability to form biofilms [3,4] and thus can be difficult to manage [5]. *Enterococcus faecium*is listed as one of the ESKAPE (an acronym for *Enterococcus faecium, S. aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter spp.*) organisms, which are resistant to a majority of antibiotics available in our arsenal [6,7].

There is a lack of high quality randomized, controlled, prospective comparative treatment studies. However, based on the high failure rate of Enterococcal PJIs and the known limited bactericidal activity of ß-lactams on enterococci, some authors have suggested the use of combination antibiotic therapy for management of patients with enterococcal PJIs [8]. However, another study demonstrated that patients who received monotherapy had the same outcome as those treated using combination therapy regimen [9]. El Helou et al. described an 80% success rate using debridement, retention of the implant and intravenous ampicillin with or without gentamicin [9]. The success rate was similar in the monotherapy and combination groups, but nephrotoxicity was significantly higher among those receiving aminoglycosides. The results of the multi-institutional study by Kheir et al. support the former recommendation of combination systemic therapy [1]. Although the authors did not find statistical significance, there was a trend toward higher treatment success with combination antibiotic therapy. In addition, there is a high risk of selection bias in retrospective studies evaluating the efficacy of antibiotic therapy, as dual therapy is often applied in more severe infectious cases. The efficacy of dual theraphy in Enterococcal infections in clinical studies is primarily demonstrated for Enterococcal endocarditis. For monomicrobial non-resistant *E. faecalis* and *E. faecium* PJI, we recommend a combination of an intravenous cell wall synthesis-inhibiting agent (ampicillin or vancomycin, respectively) and to add gentamicin as a synergistic antibiotic, at least during the first two weeks of treatment, which is concordant with previous literature [1,5,10,11]. It is important to note that administration of a systemic aminoglycoside can increase the risk of nephrotoxicity and ototoxicity [9]. Other alternatives suggested in the literature to include as a synergistic antibiotic (instead of gentamicin) are ceftriaxone [12] or daptomycin [13-15]

Interestingly, it has also been suggested that rifampin in combination with other antibiotics may also lead to a lower rate of failure in early Enterococcal PJIs. Tornero et al. found that the administration of rifampin combined with other antibiotics was associated with a lower rate of failure than alternative antibiotics [16]. In addition, recent in vitro data showed that linezolid or ciprofloxacin combined with rifampin had better activity against Enterococcal biofilms than ampicillin or ampicillin plus rifampin; therefore, these combinations are potential alternatives [17].

Emerging antibiotic resistance, specifically to vancomycin, is a challenging problem for the management of Enterococcal PJIs [5,18]. Plasmid-mediated resistance to vancomycin was first described in 1986, and shortly thereafter numerous reports of the vancomycin-resistant *Enterococcus* (VRE) species appeared in the literature [19]. VRE species are phenotypically and genotypically heterogeneous, and among all of these phenotypes and genotypes, VanA resistance phenotype has been most commonly investigated [19]. For VRE, the literature suggests the use of either linezolid (with or without rifampin) [17] or daptomycin [1,20]. Although linezolid-resistance has been reported, fortunately at present there is no report of emerging daptomycin-resistant *Enterococcus* [21–24].

Polymicrobial infections are challenging to treat, as administration of multiple antibiotics is often needed [25]. For polymicrobial infections, broad-spectrum coverage should be performed. Literature is sparse on the use of oral antibiotics for patients with polymicrobial enterococcal PJIs, and it is not known if oral antimicrobial can be used for successful treatment of these patients.

The review of the available literature revealed that there was a high variability of antibiotic treatment duration for Enterococcal infections and lack of analysis regarding treatment duration in the above studies. In the study by Kheir et al., each patient's antibiotic duration was listed, and the majority of patients had six weeks of antibiotic treatment (although the range was broad: from 4-36 weeks of duration) [1]. Duijf et al. reported three months of antibiotic treatment resulting in 66% of patients retaining their implants [26]. This may suggest that longer antibiotic treatment may be beneficial in Enterococcal PJIs;however, further study is warranted in this domain.

Based on the available literature, and our experience, we recommend that patients with Enterococcal PJIs should be treated with 6-12 weeks of antimicrobial agents, preferably in combination.

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QUESTION 9: What are the indications for utilizing fosfomycin, tigecycline and daptomycin, either instead of other antibiotics or in conjunction with other antibiotics, for the management of periprosthetic joint infections (PJIs)?

RECOMMDENATION FOR DAPTOMYCIN: Daptomycin is an alternative treatment for patients with PJIs caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

LEVEL OF EVIDENCE: Moderate

RECOMMENDATION FOR FOSFOMYCIN: Although there is no clinical experience using fosfomycin in PJIs, it could be considered in infections due to multi-drug resistant gram-positive (MDR-GP) or gram-negative bacteria (GNB) as a part of a combination regimen with daptomycin, rifampin or tigecycline when the microorganism is susceptible.

LEVEL OF EVIDENCE: Limited

RECOMMENDATION FOR TIGEYCYLINE: Tigecycline could be considered for the treatment of MDR-GP or -GNB as a part of a combination regimen when the microorganism is susceptible.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 4%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

Daptomycin

Daptomycin is a cyclic lipopeptide with concentration-dependent bactericidal activity against gram-positive microorganisms. It is highly active against *Staphylococcus aureus*, coagulase-negative Staphylococci, *Enterococcus faecalis* and *Enterococcus faecium*, including both planktonic and biofilm-embedded bacteria [1]. Daptomycin combined with gentamicin has been shown to have synergistic activity on intracellular *S. aureus*. Additionally, daptomycin seems to exhibit activity against the stationary-phase bacteria inside a biofilm [2–4]. Several animal models of foreign-body infection demonstrated a high success rate with daptomycin but always in combination with rifampin [5,6].

Since its commercialization, several case series and one clinical trial have evaluated the efficacy of daptomycin in PJIs (Table 1). The first description [7] included 12 patients that received 4 mg/kg of daptomycin in monotherapy with a success rate of 45.5%. In addition, out of the five patients considered a success, only one retained the implant with oral suppressive therapy. Byren et al. [8] performed a

prospective, randomized controlled trial in PJIs treated with two-stage exchange to evaluate the safety and efficacy of 6 or 8 mg/kg of daptomycin in monotherapy for six weeks compared with the standard-of-care (vancomycin, teicoplanin or semisynthetic penicillin). A total of 75 patients were included and the clinical success rates were higher in daptomycin groups than in control group (58.3% for 6 mg/kg daptomycin vs. 60.9% for 8 mg/kg daptomycin vs. 38.1% for the comparators). The frequency of adverse events was similar in both groups; however, 16% and 22% of the patients in the 6 mg/kg and 8 mg/kg of daptomycin had increased creatine phosphokinase (CPK) levels (>500 U/L) vs. 8% in the control group.

In a retrospective study, Corona et al. [9] described 20 patients with PJI who received an average daptomycin dose of 6 mg/kg/day for a mean duration of 44.9 days. Fourteen patients were evaluated and four received rifampin (28.6%). The remission rate was higher than in previous studies (78.6%) and all patients treated with rifampin (including three acute PJI treated with debridement, antibiotic and implant retention (DAIR)) were in remission. Noteworthy, severe side effects occurred in two patients (10%) receiving daptomycin without rifampin and both required admission to the ICU. One developed a daptomycin-induced eosinophilic pneumonia and the other developed a massive rhabdomyolysis with acute renal failure. For this reason, authors recommended close monitoring for symptoms of myopathy with a weekly serial follow-up of serum creatinine. In addition, Jugun et al. [10] evaluated prospectively 16 patients with an osteoarticular infection treated with 8 mg/kg/day of daptomycin plus 600 mg of rifampin for a median duration of three weeks. Only six had a PJI but no clinically or laboratory-documented adverse events occurred that required adjustment or discontinuation of daptomycin therapy. All patients were in remission after an average of 15.8 (range 12.4-30) months of follow-up. Lora-Tamayo et al. [11] performed a retrospective, multi-centric study to evaluate the efficacy and safety of a 6-week course of daptomycin at 10 mg/kg plus rifampin in 20 patients with acute staphylococcal PJI managed with DAIR. Results were compared with 44 matched historical controls with PJI caused by fluoroquinolone-resistant staphylococci. The clinical failure rate was 50% in daptomycin group vs. 34% in historical controls (p = 0.265) and 29% and 30% had microbiological failure, respectively.

Malizos et al. [12] evaluated all patients with osteoarticular infection retrospectively collected from the European Cubicin® Outcomes Registry and Experience (EU-CORE) study that registered

TABLE 1. Summary of the clinical experience with daptomycin in PJIs including case series with more than five cases

Author, Year	Type of Study	Numberof Patients/ Type of PJI - Surgical Treatment	Dose, Duration	Rifampin (%)	Adverse Events Related with Daptomycin (%)	Follow-up Months (range)	MRSA n/Total (%)	Remission n/ Total Evaluated (%)
Rao 2006 [7]	P	12 / 5 early acute-DAIR 7 chronic-2S	4 mg/kg, 6 weeks	0	0	9 (range 7-13)	7/12 (58.3)	5/11 (45.5)
Byren 2012 [8]	RCT	75 / chronic-2S	6 mg/kg vs. 8 mg/kg vs. control, 6 weeks	0	CPK >500 u/L 6 mg/kg: 16% 8 mg/kg: 21.7% control: 8%	5-7	3/25 (12) 7/24 (30.4) 3/25 (12)	6 mg/kg: 14/24 (58) 8 mg/Kg:14/23 (61) control: 8/21 (38)
Corona 2012 [9]	R	20/ 8 early acute-5 DAIR and 3 2S 12 chronic-9 2S and 3 1S	6.6 mg/kg (median), 6.4 weeks	yes:8 (40)	CPK: 1 (12.5)	20 (range 12-41)	1/14 (7.1)	Acute infection: 5/6 (83.3) Chronic infection: 5/7 (71.4)
				no:12 (60)	CPK: 1 (8.3) Eosinophilic pneumonia: 1(8.3)			
Jugun 2013 [10]	P	16 osteoarticular infection (6 withPJI)	8.15 mg/kg (median) + rifampin 600 mg/d, 7.3 (range 2-17) weeks	16 (100)	0	15.8 (range 12.4-30)	3/6 (50)	totally or partially removed: 3/3 (100) DAIR: 3/3 (100)
Lora-Tamayo 2014 [11]	R	20 early acute-DAIR	10 mg/kg + rifampin 600 mg/d, 6 weeks	20 (100)	Rhabdomyolysis: 1 (5)	25 (range 24.4-32.3)	10/18 (55.5)	Daptomycin + Rifampin: 9/18 (50) Control group: 15/44 (34)
Chang 2017 [16]	R	16 / 5 early acute-DAIR 11 chronic-2S	8.3 mg/kg, 2 weeks	0	0	27	10/16 (62.5)	2S: 10/11 (91) DAIR: 4/5 (80)

P, prospective cohort; RCT, randomized control trial; R, retrospective cohort; PJI, prosthetic joint infection; MRSA, methicillin-resistant *S. aureus*; DAIR, debridement and implant retention; 2S, two-stage exchange; 1S, one-stage exchange.

real-world outcome data from patients receiving daptomycin. Out of 638 patients, 432 (67.7 %) had osteomyelitis and 206 (32.3%) had an orthopaedic device infection. More than 75% of the patients received ≥ 6 mg/kg of daptomycin during a median of 16 days (range, 1-176) for orthopaedic device infections. The remission rate was 81.8% overall and 85% in patients with PJI. Unfortunately, data about the type of infection (acute or chronic), methicillin-resistant *Staphylococcus aureus* (MRSA) rate and the surgical management was not reported. Overall, adverse events were reported in 78 (12.2%) patients, being severe in 39 (6.1%) and requiring discontinuation in 35 (5.5 %). The most recent report is a retrospective description of 16 patients treated with high doses of daptomycin (8.3 mg/kg per day) in monotherapy during a median of 14 days [13]. After this, all patients received oral antibiotics during a median of 35 days. The oral antibiotic combinations included were sulfamethoxazole/trimethoprim plus rifampin or fusidic acid plus rifampin. The study included 5 patients with an acute PJI treated with DAIR and 11 with a chronic PJI treated with two-stage exchange. It is important to highlight the high percentage of methicillin-resistant *S. aureus* (MRSA) (62.5%) and the high remission rate (87.5%). Specifically, there was one failure in acute PJIs (20%) and one among chronic ones (9%), both due to MRSA. No serious adverse events were reported.

In conclusion, a clinical trial showed that daptomycin at 6 or 8 mg/kg for six weeks had a higher cure rate than monotherapy with teicoplanin, vancomycin or a semi-synthetic penicillin. However, the clinical data suggest that ≥ 14 days of daptomycin in monotherapy is associated with adverse events (mainly CPK elevation). In contrast, other clinical studies combining daptomycin with rifampin did not observe problems with adverse events even after > 14 days of treatment and doses up to 10 mg/kg. This data suggests that rifampin could reduce the serum concentration of daptomycin (substrate of glycoprotein-P) but more data is necessary to support this hypothesis [13]. On the other hand, a short course of high dose (≥ 8 mg/kg) daptomycin without rifampin for the first two weeks of treatment followed by an oral rifampin combination seems to be well tolerated and associated with good outcome. Recent data show that the addition of daptomycin to cloxacillin or cefazolin may provide synergy, as shown by in vitro studies and animal experimental models [5,14]. This combination is promising to avoid the use of rifampin during the first 1-2 weeks of antibiotic treatment and to reduce the risk of selecting daptomycin-resistant mutants [15].

Fosfomycin

Fosfomycin has a broad-spectrum, including MDR-GP and (gram-negative (GN) microorganisms, a time-dependent bactericidal activity andis maintained in a low pH and in anaerobiosis [17–19]. Fosfomycin has a high bone penetration (bone:serum ratio of 43%), achieving concentrations above the minimum inhibitory concentration (MIC) for most susceptible bacteria [20]. There are three presentations: sodium fosfomycin for intravenous administration and trometamol and calcium salt for oral administration. Unfortunately, the oral bioavailability is < 20% for calcium salt and < 40% for trometamol. Therefore, only intravenous antibiotic is recommended for the treatment of bone infections [21].

Against GP, fosfomycin has demonstrated a potent in vitro synergistic activity against MRSA in combination with beta-lactams, daptomycin and linezolid. In addition, in an experimental foreign-body infection, fosfomycin combined with daptomycin or with rifampin were the second and the third regimens with the highest cure rate (defined as the percentage of eradication from the implant) only behind daptomycin plus rifampin and this was corroborated by other authors [22–26]. However, there is no clinical data supporting the efficacy of fosfomycin in PJI due to GP.

Fosfomycin has bactericidal activity in combination with carbapenems and colistin against carbapenemase-producing *Klebsiella pneumoniae* [27,28]. Corvec et al. [29] evaluated the activity of fosfomycin and tigecycline alone or in combination with other drugs against extended-spectrum beta-lactamase (ESBL) producing *Escherichia coli* strains in a foreign-body infection model. Fosfomycin was the only single agent for which the eradication of *E. coli* from cages was achieved and the combination that showed the highest antibiofilm activity was fosfomycin plus colistin, suggesting that fosfomycin should be considered in the treatment of MDR-GNB susceptible to fosfomycin strains. It is of note that fosfomycin could decrease the nephrotoxicity of aminoglycosides that in some occasions are the only active drug [30]. Although there is no clinical experience using fosfomycin in PJI due to GNB, it should be considered in infections due to MDR-GNB as a part of a combination regimen when the microorganism is susceptible.

Tigecycline

Tigecycline is active against GP and GN (except *Pseudomonas),* including vancomycin-resistant enterococci, MR-staphylococci, ESBL producing, carbapenemase (CP)-producing *Enterobacteriaceae* and *Acinetobacter* spp. Tigecycline has demonstrated synergistic activity against *Enterococcus* spp combined with rifampin and with amikacin or colistin against some MDR-*Enterobacteriaceae* spp, *Acinetobacter baumanii* or *Stenotrophomonas maltophilia* [31]. Data from foreign-body infection models due to MRSA showed that tigecycline in monotherapy was similar to vancomycinand in combination with rifampin was as effective as vancomycin with rifampin. Both options avoid the selection of rifampin-resistant mutants [32,33]. A recent study in healthy volunteers undergoing elective orthopaedic surgery demonstrated a good bone penetration after multiple doses of tigecycline (bone:serum ratio of 4) [34].

Clinical experience in osteomyelitis with tigecycline was documented in 13 cases with success in 85% but only one case was associated with an orthopaedic implant. In PJI the level of evidence is limited to a few case reports [35]. Vila et al.described three patients with early PJI of total hip arthroplasty due to MDR *A. baumannii* treated with debridement, implant retention and a high dose of tigecycline (100 mg every 12 hours) [36]. All patients received colistin concomitantly during a mean of 8.7 days and required at least one additional debridement, but all were asymptomatic after a median of 2.5 years. The major limitation for the prolonged use of tigecycline is the high frequency of nausea and vomiting. Vila et al. diluted tigecycline in 400 mL of dextrose and administered at a slow infusion rate in order to reduce the adverse events, and the therapy was well tolerated.

In contrast, de Sanctis evaluated three patients with a PJI due to carbapenem-resistant *K. pneumoniae* with poor outcomes [37]. All were polymicrobial infections, required multiple surgeries and complex antibiotic courses including tigecycline (two cases in monotherapy and one combined with amikacin first and with colistin later on). Prostheses were removed in two cases, but those patients died, and the one who survived required salvage limb amputation. In addition, resistant mutants to colistin and amikacin were selected while on antibiotic treatment however, the dose of tigecycline was not reported. Furthermore, Asseray et al. described four patients with PJI due to MDR- GP managed with implant removal and tigecycline during a median of 105 days (range 90-150) [38]. In addition, two patients received concomitant treatment with fosfomycin and one with linezolid. All patients but one (75%) were in remission after an average of 20.2 (range 14-32) months of follow-up. Only one patient treated with tigecycline plus fosfomycin experienced a moderate adverse event with anemia and thrombocytopenia, which was not

attributed with certainty to tigecycline; however, the dose of tigecycline was not specified. The rationale for increasing the dose (100 mg/12 hr) is based on its pharmacodynamic properties (area under the curve to minimum inhibitory concentration (AUC/MIC) ratio is the most predictive parameter related to clinical and microbiological efficacy), the presence of biofilms, and the multidrug-resistant profile of the involved organism [39]. Further experience and clinical studies are necessary, but tigecycline should be considered for the treatment of MDR-GP or GNB as a part of a combination regimen when the microorganism is susceptible.

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5.10. TREATMENT: ANTIMICROBIALS (TWO-STAGE)

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QUESTION 1: (A) What is the optimal length of administration for antibiotic treatment following resection arthroplasty? (B) What is the optimal mode of administration for antibiotic treatment following resection arthroplasty?

RECOMMENDATION: Antimicrobial therapy should be individualized and based on the sensitivity profile of the microorganism, patient tolerance and drug side-effect profile. There is no conclusive evidence supporting the exact length of antibiotic therapy after resection arthroplasty. We recommend treatment for two to six weeks. Either intravenous, oral antibiotics, or a combination are acceptable for treatment following resection arthroplasty as long as the oral agent has adequate bioavailability and can achieve a concentration at the site of infection to eradicate the infecting organism, if used alone.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 87%, Disagree: 9%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

Treatment of periprosthetic joint infections (PJIs) with a two-stage revision arthroplasty remains a widely-used treatment strategy with success rates ranging from 72-94% [1–6]. The use of an antibiotic regimen after the initial explantation and placement of an antibiotic spacer is common; however, the optimal length and route of antibiotic administration has yet to be determined. Ensuring identification of the organism(s) prior to antibiotic therapy is critical for appropriate tailored treatment. Prior studies have shown that culture-negative patients that meet the MusculoSkeletal Infection Society (MSIS) criteria for PJI are difficult to treat and have been associated with 4.5 times increased risk of reinfection when compared to those patients where an organism was identified by culture [5,7]. In a recent study, culture-negative patients who met the MSIS criteria were investigated using next-generation sequencing and an organism was identified in 81.8% of samples, with the majority being low virulent organisms [8]. Understanding the infecting organism(s), the virulence patterns and their antibiotic susceptibilities by region are critical aspects to successful selection and chosen duration of antibiotics.

The literature has not found prolonged antibiotic therapy beyond six weeks to significantly increase success rates, and it may increase the rate of antibiotic related complications and expenses [9–11]. Many published studies have reported success rates ranging from 88-100% with a combination of oral and intravenous (IV) antibiotic administration of six weeks or less [6,12–18]. Bernard et al. found that the cure rate was no better with 12 weeks of antibiotics compared to 6 weeks for 144 knee and hip PJIs, including 74 resection arthroplasties [10]. Median IV antibiotic therapy was 10 days in the patients treated with two-stage exchange in this study [10]. Hsieh et al. evaluated the use of a total of 4-6 weeks of IV antibiotic therapy as compared to one week of parenteral antibiotic therapy in 99 two-stage revision total hip arthroplasty (THA) patients [14]. They found a 91% infection cure rate at final follow-up in patients treated with 4-6 weeks of antibiotic therapy and an 89% cure rate in patients treated for one week [14]. Treatment of antibiotic-resistant organisms for more than six weeks has also not been shown to improve outcomes. In one retrospective study, total knee arthroplasty (TKA) periprosthetic joint infection (PJI) patients infected with methicillin-resistant *Staphylococcus aureus* and streptococcal organisms had similar success rates with IV antibiotic therapy less than six weeks as compared to greater than six weeks when treated with a two-stage exchange [13].

To our knowledge, no published study has compared the efficacy of oral-only vs. IV-only antibiotics after resection arthroplasty, but a current study is underway [19]. Thus, antimicrobial treatment is mainly started with intravenous antibiotics in order to quickly achieve the appropriate concentrations locally. Once this initial postoperative scenario has improved, switching to oral antibiotic regimens is considered. Yet, an increasing number of clinicians and surgeons are using a combination approach of IV and oral antibiotics following resection arthroplasty, including some using rifampin as a companion drug [20–22]. Darley et al. described success in a small series of infected THAs using a median of 14 days of IV antibiotics (range, 12-28 days) followed by oral antibiotics for a median of 6 weeks (range, 2-25 weeks) before second-stage reimplantation, often in combination with rifampin [21]. Bassetti et al. described success with an "Udine strategy" following resection arthroplasty, particularly for gram-positive PJIs where an IV glycopeptide/lipopeptide plus rifampin is used for two weeks followed by four weeks of oral linezolid, and all therapy stopped at six weeks as long as two serial weekly C-reactive protein (CRP) levels are normal [20]. Currently, the Infectious Diseases Society of America (IDSA) recommends 4-6 weeks of pathogen-specific IV or highly bioavailable oral antimicrobial therapy following resection arthroplasty with an A-II recommendation [23]. However, many panel members would use six weeks of therapy for more virulent organisms such as *S. aureus* [23]. Similarly, an Italian guideline recommends that following resection arthroplasty, antibiotics be given 2-3 weeks parenterally, and 5-6 weeks orally with consideration of 6-weeks IV therapy without any retained foreign material for difficult-to-treat microorganisms [24]. Additionally, recent guidelines by the Spanish Society of Infectious Disease and Clinical Microbiology are similar to prior societal guidelines and recommend 4-6 weeks of pathogen-specific intravenous or highly bioavailable oral antimicrobials after resection arthroplasty [25].

In conclusion, there is no consensus on the exact length or route of antibiotic therapy in patients undergoing resection arthroplasty. The use of antibiotic therapy for 4-6 weeks after resection arthroplasty is supported by current studies and infectious disease societies. While some evidence has suggested an even shorter duration may be just as efficacious, further research will be required. A limited duration of IV antibiotic therapy may be indicated alone, in conjunction with oral antibiotics, or followed by oral antibiotics if organism-specific, highly bioavailable, oral antibiotics are available

for continued therapy and if agreed upon after discussion by a multidisciplinary team.

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QUESTION 2: Does extended oral antibiotic prophylaxis following reimplantation reduce the risk of future failure? If so, what type of antibiotic should be administered and for how long?

RECOMMENDATION: Possibly. There is emerging evidence that administration of three months of oral antibiotics directed towards the original infecting organism following reimplantation reduces the risk of early failure secondary to periprosthetic joint infections (PJIs).

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 76%, Disagree: 18%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

PJIs are one of the most devastating complications following hip and knee arthroplasty and are associated with significant morbidity and mortality [1–3]. Several approaches have been used to treat this complication, one being a two-stage exchange arthroplasty with placement of an antibiotic-impregnated spacer followed by directed antibiotic therapy [4]. Hanssen et al. reported a 90% success rate with a two-stage exchange arthroplasty approach [4]. More recent studies have shown higher failure rates with this treatment modality due to reinfection with either the same or with a new organism [5–7].

To address the question of whether antibiotic treatment following reimplantation surgery had any effect on the subsequent failure rate, we conducted an extensive literature search. After removal of duplicates, 111 articles were found. After review of the abstracts, 52 additional articles were excluded. The remaining 59 articles were reviewed, among which 3 original scientific publications compared an extended course of postoperative antibiotics following a two-stage exchange.

All three studies were current, with publication dates ranging from 2011 to 2016. Study populations ranged from 66-107 patients. The highest quality study was a multicenter prospective randomized controlled trial. Two retrospective studies have evaluated the use of prophylactic antibiotics following reimplantation. Zywiel et

al. followed two cohorts of patients following a two-stage revision knee arthroplasty. Twenty-eight patients had a mean of 33 days of oral antibiotics (range, 28-43 days) following the reimplantation procedure and 38 patients received between 24 and 72 hours of post-operative intravenous antibiotics as standard prophylaxis. Patients were followed over a 12-month period and evaluated for reinfection. They found that the risk of reinfection with extended oral antibiotics was 4% compared with 16% in the control cohort that received routine perioperative antibiotics [8]. The single patient who was reinfected in the oral prophylaxis cohort was found to be infected with methicillin-resistant *Staphylococcus aureus*, which was present at the time of the original component removal. In contrast, a variety of low virulence organisms were the cause of reinfection in the group that received short-term prophylactic antibiotics intravenously. In a study by the same group that examined patients treated for periprosthetic hip infections, Johnson et al. found a 13.6% rate of reinfection in the perioperative antibiotic group compared to 0% reinfection in those patients treated with oral antibiotics for 14 days following a two-stage exchange [9].

There is presently one randomized controlled trial that reported the use of prolonged prophylactic oral antibiotics following reimplantation [10]. This multi-institutional study randomized patients to receive three months of oral antibiotics or standard prophylactic intravenous antibiotics only for up to 72 hours. This study included a total of 107 patients who were undergoing a two-stage revision hip or knee arthroplasty for a periprosthetic infection that met the MusculoSkeletal Infection Society (MSIS) criteria at the first stage and with negative cultures at the second stage. The rate of reinfection was 19% in the control group compared to 5% in the treatment group ($p = 0.0162$). Eight of the nine infections in the control group and one of the three in the extended oral antibiotic group were infections associated with a new organism. In the antibiotic cohort, three patients had to stop their antibiotic due to adverse reactions such as gastrointestinal upset and nausea. Three additional patients had minor adverse reactions such as rash or yeast infection; however, they continued to take the oral antibiotic despite these side effects.

Based on the available literature, there is moderate evidence to suggest that relatively short (three months) courses of oral antibiotic, following reimplantation after a two-stage exchange may reduce early failure with reinfection. All studies evaluating the role of antibiotic suppression have been short term and longer follow-up of the same cohort is needed as the one randomized trial did not report a full two years of follow-up for all enrolled patients. In addition, it is important to note that there were some issues with the administration of antibiotics and some patients had to discontinue the antibiotic. Administration of antibiotics under any circumstances needs to be weighed against its harm to the patient in terms of adverse effects and harm to society in terms of cost and its potential to cause emergence of resistant organisms.

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QUESTION 3: When is the optimal time to change intravenous (IV) antibiotic(s) to an oral agent(s) after a resection arthroplasty as part of two-stage exchange?

RECOMMENDATION: There is evidence to support pathogen-specific, highly bioavailable oral antibiotic therapy as an appropriate choice after resection arthroplasty in a two-stage treatment of periprosthetic joint infections (PJIs) after an initial IV antibiotic period of at least 5-7 days.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 83%, Disagree: 14%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

Resection arthroplasty with a two-stage exchange is utilized in the management of PJIs in patients who are not candidates for a one-stage exchange, are medically able to undergo multiple surgeries and in whom the surgeon believes that replantation arthroplasty is possible [1]. An important part of the exchange arthroplasty includes administration of systemic antimicrobial therapy. The optimal time and the mode of administration of systemic antimicrobials has been the subject of numerous studies, with no definitive recommendations available.

Several studies recommend 4-6 weeks of pathogen-specific IV or highly bioavailable per oral (PO) antimicrobial therapy for patients with PJIs who have undergone two-stage exchange arthroplasty [1–3].

PJIs are usually treated with IV antibiotics in order to obtain the ideal plasma concentration in the shortest time possible. IV therapy requires an intravenous vascular access line that can be associated with infections and thromboembolic diseases [4]. Changing to PO therapy is less invasive for patients, lowers the financial burden and reduces hospital stay. Because of the aforementioned attributes of oral antibiotics, there has been an interest in identifying patients who may be candidates for administration of oral antibiotics.

Currently, there are no high-quality studies comparing different periods of initial IV regimens. An initial short course of IV therapy can reduce bacterial bioburden and minimize the risk of emergence of antimicrobial resistance [5–7]. Changing to PO therapy to complete the course of treatment has been shown to be effective. Darley et al. showed that 10-14 days of IV antibiotic therapy followed by 6-8 weeks of PO therapy was successful in 17 patients who underwent two-stage resection arthroplasty for management of prosthetic hip infections [8]. Ciriviri et al. and Ascione et al. showed high success rates with a similar approach [9,10]. Studies have also shown success with 5-7 days of IV therapy followed by PO therapy [11–13]. A fall in C-reactive protein (CRP) value was used to guide the timing for change in one study [14]. Observational studies using only shortened IV antibiotic courses in patients with antibiotic cement spacers have also reported success [15,16]. Of note, in examining the treatment of chronic osteomyelitis in adults, a Cochrane review of 5 small trials of 180 participants with bone or joint infection showed no benefit to IV therapy as compared to PO therapy [17].

Prospective, randomized clinical trials examining the role of PO antibiotic therapy for bone and joint infection are needed. The recently published results from the OVIVA (oral versus intravenous antibiotic treatment for bone and joint infections) trial was an important contribution. This study was a parallel group, randomized (1:1), un-blinded, non-inferiority trial conducted in 30 hospitals in the United Kingdom comparing PO to IV antibiotic treatments for bone and joint infections. Both arms had six weeks of either PO or IV antibiotics, and those selected for the PO arm had seven days or less of IV antibiotics at the start of treatment. A pilot of 228 participants that concluded in 2013 supported extension to the multicenter trial. The final analysis of 1,015 participants concluded that PO antibiotic therapy was non-inferior to IV therapy when used during the first 6 weeks in the treatment of bone and joint infections, as assessed by treatment failure within 1 year of randomization [18]. The study included 302 participants who underwent resection arthroplasty or implant removal. Additionally, a prospective study looking at extended PO antibiotics after second-stage (reimplantation surgery) showed a decreased rate of reinfection [19].

Given the availability of highly bioavailable PO antibiotic agents with good tissue penetration, the strategy of a shortened initial IV antibiotic course followed by pathogen-specific PO therapy should be considered following resection arthroplasty as part of two-stage exchanges. Additional prospective studies comparing outcomes to extended IV therapy should help clarify the optimal timing for transition. However, based on the available evidence it appears that oral administration of an antimicrobial, at least after a short period of IV treatment, is a viable option in treatment of some patients with PJIs and should be considered.

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QUESTION 4: Can short term (two weeks or less) antibiotic treatment be considered following resection arthroplasty for chronic periprosthetic joint infections (PJIs)?

RECOMMENDATION: Yes. Following an aggressive debridement and insertion of an antibiotic-loaded cement spacer (ALCS) or beads, a short-term course of less than two weeks of systemic antibiotic therapy can be considered. Several studies show promising results with infection eradication rates comparable to when a much longer course of antibiotic treatment is used.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 64%, Disagree: 32% Abstain: 4% (Super Majority, Weak Consensus)

RATIONALE

Successful management of PJIs requires appropriate surgical intervention with additional antibiotic therapy. PJIs can be treated by several surgical strategies that range in invasiveness, including debridement and irrigation of the infected prosthesis, one- to two-stage exchange with or without the placement of a spacer or an extension device, resection arthroplasty and amputation. However, the ideal duration of antibiotic therapy, intravenous (IV) alone or combined IV and oral antibiotics, is not known. With increasing concerns about the emergence of antibiotic resistance and the spiraling costs of healthcare worldwide, shorter courses of antibiotic therapy, if equally efficacious to the more traditional 6- to 12-week course, would be a very attractive proposition.

The rationale of using a shortened duration of systemic antibiotics is based on the high local levels of antibiotic that can be achieved following elution from antibiotic-loaded bone cement, whether this is in the form of spacers or cement beads. Local tissue levels of antibiotic are above the minimum inhibitory concentration (MIC) for commonly infecting organisms [1–3] (Tables 1 and 2), and the levels are greater than that which can be achieved with IV administration alone.

Although some groups have reported good clinical outcomes with meticulous debridement and combinations of local and short-term systemic antibiotic therapies, most of the studies examining short-term inter-stage antibiotic treatments were retrospective cohort studies on a small number of patients. There were very few studies in which antibiotic therapy was less than two weeks duration. In addition, there was significant inter-study heterogeneity in the definition of infection, in the treatment approach with regard to the debridement method, in differing combinations of systemic and ALCSs and in the antibiotic therapy after reimplantation. Although the results appear promising, the inter-study heterogeneity makes it difficult to utilize the studies as collective evidence to support short-term inter-stage antibiotic treatment.

In a small randomized controlled trial that did not meet Consort guidelines, Nelson et al. compared inter-stage treatment with antibiotic-laden cement beads, combined with no more than five days of inter-stage systemic antibiotic therapy, to traditional inter-stage systemic antibiotic therapy alone in 26 patients treated for PJIs with two-stage resection arthroplasties. All patients were reimplanted at 6 weeks following stage-I surgery. After a mean follow-up period of 32 months, infection eradication was 100% in the group treated with antibiotic-laden cement beads and 93% in the group treated with systemic antibiotics alone [4].

In a retrospective cohort study, McKenna et al. assessed the effectiveness of a five-day inter-stage course of systemic vancomycin combined with an ALCS containing vancomycin, gentamicin, and tobramycin, following resection arthroplasty for failed total knee arthroplasty (TKA) due to PJIs in 30 consecutive patients. At the gentamicin of reimplantation (mean = 16 days) no infection recurrence was reported. A second five-day course of systemic antibiotics was administered following second-stage reimplantation. At a mean follow-up of 35 months, infection eradication remained at 100% [2].

In a retrospective cohort study, Whittaker et al. assessed a two-week inter-stage course of systemic vancomycin combined with a vancomycin and gentamicin loaded spacer, for hip PJIs. Three patients required a repeat debridement prior to reimplantation due to recurrent infection (7%). Of those patients receiving second-stage reimplantation, 92.7% were infection-free at a mean follow-up of 49 months [5].

Hoad-Reddick et al. reported on a retrospective cohort study that included 38 patients who underwent staged exchange with a combination of ALCS, antibiotic-laden cement (ALC) beads (loaded with vancomycin, gentamicin or both) and broad-spectrum prophylactic systemic antibiotics administered at 8 and 16 hours with no further systemic antibiotics given. Infection eradication after second-stage reimplantation at a mean follow-up of 56.4 months was 89% [6].

In a retrospective cohort study that included 107 patients with hip PJIs (36 of which had recurrent PJIs), Hseih et al. compared outcomes of 56 patients treated with one week of inter-stage IV antibiotic therapy to outcomes of 51 patients treated with 4-6 weeks of IV therapy, followed by two additional weeks of oral antibiotic therapy after reimplantation. Both groups also had antibiotic-impregnated spacers. Infection eradication was achieved in 92.4% (1 week) and 91.3% (4-6 weeks) of patients, respectively at a mean follow-up time of 43 months (range = 24-60 months) [7]. The number of patients in these studies who were infection-free after completing the two-stage procedure ranged from 86.7-100%, comparable to the rates achievable with a standard 4- to 6-week antibiotic regimen.

Appropriate usage of antibiotics is of paramount importance, more so today than ever, in view of emerging antibiotic-resistant organisms. Short-term therapies (i.e., less than two weeks) can be considered when managing patients with PJIs. However, prospective randomized controlled trials are needed to further explore this issue.

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TABLE 1. Therapeutic ranges and minimum biofilm eliminating concentration (MBEC) values for various antibiotics

Antibiotic	Therapeutic Peak (mg/L; µg/mL)	MBEC (mg/L; µg/mL)				
		S. aureus	*MRSA*	*P. aeruginosa*	*S. epidermidis*	*E. coli*
Azithromycin	0.3 - 0.6		5120	2560		
Ceftazidime	< 150			2560 - 5120		
Ciprofloxacin	2.5 - 4		256 - 1280	80 - 1280		
Clindamycin	< 0.5		64 - > 1024			
Colistin	1 - 4			160 - 2560		
Daptomycin	6 - 10	600	1014			
Doxycycline	< 10		64 - 128			
Erythromycin	0.5 - 3	6400	64 - > 1024	2560		
Gentamicin	5 - 10	6400	1 - > 256	512xMIC		
Linezolid	0.5 - 4	6400	4 - > 1024			
Piperacillin	5 - 20			> 5120		
Tobramycin	5 - 10	160 - 4000	≥ 8000	250 - 2000	≥ 8000	62.5 - 125
Vancomycin	25 - 50	2000 - 8000	2000 - 8000		1000 - 8000	

MBEC, minimum biofilm eliminating concentration; MRSA, methicillin-resistant *Staphylococcus aureus*

TABLE 2. Peak local antibiotic concentrations via cement elution

Study	Cement Protocol	Peak Joint Concentrations
Masri et al. [8]	ALCS: 1.2 - 4.8 gm of tobramycin and 1 - 2 gm of vancomycin per 40 gm pack	1.25 - 16.97 mg/L
Hsieh et al. [7]	ALCS: 4 gm vancomycin powder and 4 gm aztreonam per 40 gm pack	vancomycin: 1538 mg/L; aztreonam: 1003.5 mg/L
Anagnostakos et al. [9]	ALCS + beads: 1 gm gentamicin and 4 gm vancomycin per 40 gm pack	gentamicin: 115.70 mg/L; vancomycin: 80.40 mg/L
Fink et al. [10]	ALCS: 'Pre-prepared' mix	gentamicin: 50.93 mg/L; vancomycin: 177.24 mg/L; clindamycin: 322.29 mg/L

ALCS, *antibiotic-laden* cement spacer

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5.11. TREATMENT: ANTIMICROBIAL SUPPRESSION

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QUESTION 1: Is there a role for administration of prolonged oral antibiotics following primary total joint arthroplasty (TJA)?

RECOMMENDATION: No. The administration of prolonged oral antibiotics in the context of perioperative prophylaxis after primary TJA is not recommended. Continuing antibiotic prophylaxis longer than 24 hours after wound closure has not proven to be beneficial; indeed, it may contribute to the development of antimicrobial resistance, carries risks and adds to healthcare costs.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

The use of preoperative systemic intravenous antibiotic prophylaxis reduces the risks of postoperative infections in TJAs. Numerous guidelines, including those developed jointly by the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), the Surgical Infection Society (SIS) and the Society for Healthcare Epidemiology of America (SHEA) [1], all recommend preoperative antibiotic use.

The recent guidelines for the prevention of surgical site infections (SSIs) developed by the Centers for Disease Control and Prevention (CDC) state that in clean and clean-contaminated procedures, no additional antibiotics after wound closure in the operating room are necessary, even in the presence of a drain (Category IA–strong recommendation; high-quality evidence) [2]. The latter recommendation, however, is based on non-orthopaedic procedures. The American Association of Hip and Knee Surgeons (AAHKS) has funded a large randomized prospective study to examine the difference, if any, between a single dose and 24-hour dose of prophylactic antibiotics in patients undergoing TJA. While the results of the latter study are awaited, most surgeons continue to administer multiple doses of prophylactic antibiotics for patients undergoing TJA.

There are, however, numerous studies demonstrating that the use of a short course of antibiotics does not place patients at higher risks of SSIs/periprosthetic joint infections (PJIs) than longer courses of antibiotics [3–5]. A systematic review by Thornley et al. evaluated the evidence for postoperative antibiotic prophylaxis administration and its role for reduction of SSIs among patients undergoing primary total hip or knee arthroplasties [6]. The pooled estimate demonstrated that prolonged postoperative antibiotic prophylaxis did not significantly reduce the rates of SSIs (odds ratio (OR) 0.01, 95% confidence interval (CI), 0.00-0.02). However, the overall quality of the evidence was very low, owing to risk of bias, inconsistency and imprecision in the studies evaluated [6].

There has been minimal work performed that evaluates whether patients undergoing TJA should receive prolonged courses of oral antibiotics. A recent study presented at the annual meeting of AAHKS demonstrated significant reductions in the rates of SSIs/PJIs when prolonged (seven days) or oral antibiotic was administered to patients undergoing TJA. The study was retrospective in nature, consisted of a relatively small cohort, had a short follow-up and did not disclose the exact definition of PJIs or SSIs. Otherwise, there is no other study demonstrating that administration of prolonged oral antibiotics after TJA offers additional benefits to patients. The available evidence does not support continuation of postoperative antibiotic prophylaxis intravenously or orally for the prevention of SSIs in patients undergoing TJA.

There are numerous risks associated with the administration of antibiotics, most important of which is the realistic and sobering issue related to emergence of antimicrobial resistance (AMR). Moreover, the unnecessary use of antibiotics can lead to the development of opportunistic infections, such as *Clostridium difficile* associated diseases, that can result in extended hospital stays, increased costs for episode of care as well as higher morbidity and mortality [7].

In the absence of concrete evidence and due to the dire need for the medical community to observe antibiotic stewardship, we recommend against the prolonged use of oral or intravenous antibiotics in patients undergoing routine primary total hip or knee arthroplasty.

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QUESTION 2: What is the role of oral suppression antibiotics after reimplantation in patients with negative cultures after 14 days of incubation?

RECOMMENDATION: There may be a role for the administration of oral antibiotics to decrease reinfection rates following reimplantation in patients with negative cultures, but further study is necessary.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 73%, Disagree: 21%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

The role of oral antibiotics after two-stage revision was evaluated in one randomized controlled trial [1] as well as three retrospective studies [2–4]. Three of these studies found reduced rates of reinfection in patients who received oral antibiotics following reimplantation. One retrospective study evaluating oral antibiotics in patients with periprosthetic joint infection (PJI) included a subgroup of patients with two-stage revisions and found no differences in implant survival between the suppression and non-suppression cohorts [4]. Follow-up varied in all of the studies, with one study reporting preliminary findings, but still underway. Further more the sample size in all of these studies was relatively small and the longitudinal follow-up duration was limited.

Different antibiotics were utilized in these studies at the discretion of the treating physician, all of which have different bioavailability and antimicrobial spectrum of activity. Some of the antimicrobial therapies chosen to be administered after reimplantation are known to have bioavailability nearing 100% (e.g., fluoroquinolones, linezolid), which is more in the 'active therapy' realm vs. suppressive therapy. The original offending microorganisms also varied substantially, which could affect the results. In one study [3], 50% of the initial cultures at the time of component removal did not identify a microorganism, so these patients were treated empirically, making the choice of agent difficult. Adverse events with oral antibiotics were reported, including patients who discontinued therapy prematurely, and this should always be considered when determining whether antimicrobial therapy is appropriate for a patient.

In essence, these studies may represent a signal that the provision of oral antibiotics after reimplantation may be of benefit; however, there is a definite need to confirm these findings with further study.

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QUESTION 3: Which patients should be considered for administration of long-term suppressive oral antibiotic instead of surgical treatment in patients with chronic periprosthetic joint infections (PJIs)?

RECOMMENDATION: Long-term suppressive oral antibiotics instead of surgical treatment may be considered for patients who are not candidates for surgery, when surgery is not expected to improve the functional outcome for a patient, and for patients who refuse surgery.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

An extensive literature search was conducted to examine the role of suppressive antibiotics instead of surgical intervention for patients with chronic PJIs. No such study could be identified. To our knowledge, no study has examined specifically the profile of patients who may be considered for long-term suppressive antibiotic treatment instead of surgery for chronic PJIs.

Patients with PJIs are best treated by surgical intervention that includes the removal of infected implants or debridement of the

infected site and exchange of the modular components. The aim of the surgical intervention is to reduce the bacterial load (bioburden) and the biofilm formed on the components that cannot be penetrated by antibiotics or the immune system of the host. In some cases, however, removal of all or part of the infected implants during surgery is not in the best interests of the patient and chronic antibiotic suppression represents, in these circumstances, an unique anti-infective therapy that can be applied to these patients. The administration of antibiotics in this circumstance is meant to minimize the risk of systemic toxicities that the patient may experience as a result of proliferation of the organisms from the infective site. Another reason for administration of antibiotics in this situation is to try to keep the infection at bay by reducing drainage from the wound or the sinus tract [1–6].

The indications for the use of long-term suppressive antibiotics is not well known or well studied in the literature. In the absence of evidence, we believe that suppressive antibiotics instead of surgical intervention may be an option (1) for patients in whom surgery is contraindicated because of the patient's general condition, (2) when surgery is not expected to improve the functional outcome for patient, such as those with multiple prior failures and (3) for patients who refuse surgery.

Given the very low probabilityof obtaining remission of infection, or even control of infection, and the potential adverse effects associated with long-term antibiotics to the patient and the society, this treatment option would be best considered collegially by a multidisciplinary team working together to determine the treatment for the patient.

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Outcomes

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QUESTION 1: What is the definition of success of surgical treatment of a patient with a periprosthetic joint infection (PJI)? What clinical, operative, microbiological and functional metrics should be considered?

RECOMMENDATION: The treatment of PJIs typically does not have a dichotomous outcome. More commonly, the result is a gradient of success or failure. As such, the outcome-reporting tool has been organized into four tiers with each tier encompassing different levels of perceived success or failure. The outcomes reporting for the treatment of PJIs are the following (definitions regarding items within each tier are explained in the rationale section):

Tier 1. Infection control with no continued antibiotic therapy

Tier 2. Infection control with patient on suppressive antibiotic therapy

Tier 3. Need for reoperation and/or revision and/or spacer retention (assigned to subgroups of A, B, C, D, E, and F based on the type of reoperation)

- A. Aseptic revision > 1 year from initiation of PJI treatment
- B. Septic revision (including debridement, antibiotic and implant retention (DAIR)) > 1 year from initiation of PJI treatment (excluding amputation, resection arthroplasty and fusion)
- C. Aseptic revision ≤ 1 year from initiation of PJI treatment
- D. Septic revision (including DAIR) ≤ 1 year from initiation of PJI treatment (excluding amputation, resection arthroplasty, and fusion)
- E. Amputation, resection arthroplasty, or fusion
- F. Retained spacer

Tier 4. Death (assigned to subgroups A or B)

- A. Death ≤ to 1 year from initiation of PJI treatment
- B. Death > 1 year from initiation of PJI treatment

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 82%, Disagree: 14%, Abstain: 4% (Super Majority, Strong Consensus)

RATIONALE

The MusculoSkeletal Infection Society (MSIS) definition for PJIs provided standardization to the patient populations in PJI research [1]. As evidenced by the numerous definitions of success and failure in the literature, the same standardization has not been provided for defining the outcomes for the treatment of PJIs [2–11]. Therefore, a multi-national, multi-institutional and multi-disciplinary workgroup was organized by the MSIS to review the available evidence and propose a gold standard definition in the outcome reporting for the treatment of PJIs to improve the transparency in outcome studies and guide the definition of success for the treatment of PJIs.

Definitions and Considerations

Starting Point of Treatment Assessment

The starting point for the assessment of a treatment can influence the size of the population and alter the reported treatment success. A prior Delphi method definition of success after treatment of PJIs proposed the starting point for assessment does not begin until reimplantation surgery during a two-stage exchange [8]. However, literature on the outcomes of spacers in the treatment of PJI demonstrated that 17% of the patients underwent amputation, resection arthroplasty, arthrodesis or remained with a retained spacer instead of undergoing reimplantation [12]. The starting point for assessing the treatment of PJIs will begin at the time of the initial operation for PJIs, which will be irrigation and debridement, the first stage of a two-stage exchange or following a one-stage exchange.

Infection Control

Because bacterial organisms can undergo internalization by osteoblasts, "infection eradication" may not always be feasible and "infection control" better represents the process of treating PJIs [13]. Since the MSIS criteria for diagnosis of PJIs is simple and well established, the workgroup has defined infection control as a patient not meeting the MSIS criteria for PJIs and not having undergone or in need of further surgery (excluding the planned reimplantation of

a two-stage exchange, a procedure for a complication related to the antibiotic spacer or a planned operation to address soft-tissue issues between two-stages) [14].

Antibiotics

Given the promising results of a recent preliminary study on extended oral antibiotics after the reimplantation of a two-stage exchange, the use of antibiotics beyond the historical treatment period will become extended as more clinicians adopt this approach [15]. The workgroup has defined "off antibiotic therapy" as cessation of antibiotics within 1 year after the initial surgery. Patients are still allowed to be on antibiotics of 10 days or less for a documented infection other than PJI or antibiotics for a pre-procedure prophylaxis (i.e., dental prophylaxis or preoperative antibiotics for another operation).

Reoperation

The reasons for reoperation (excluding the planned reimplantation of a two-stage exchange, a procedure for a complication related to the antibiotic spacer or a planned operation to address soft-tissue issues between two-stages) should be reported as aseptic revisions, septic revisions or amputations, resection arthroplasties or fusions. Any patient undergoing a revision surgery who does not meet the MSIS criteria for PJIs at the time of revision is considered an aseptic revision. Aseptic revision was divided into subgroups with patients revised ≤ year or > one year from the initial surgery in the treatment for PJI. Due to advancements in DNA sequencing demonstrating higher rates of polymicrobial PJI than standard laboratory cultures, assignment of septic revision will apply to any patient revised for infection regardless of the organism [16]. Similar to aseptic revision, subgroups have been assigned based on the duration from surgery. Given some patients continue to live with the spacer, subgroup has been established for patients with a retained spacer.

Minimum Duration of Follow-up

The minimum reporting of any outcome should be 1-year follow-up. When any study reports a minimum follow-up of 1, 5 or 10 years, it will be defined as having short-term, mid-term, or long-term results, respectively.

Death

In the reporting of outcomes in Tier 4, "death" is defined as all-cause mortality with a differentiation between mortality ≤1 year or > 1 year from the initial operation for the treatment of PJIs. As more literature demonstrates the increased risk of mortality for patients undergoing treatment for PJIs, we are gaining a greater appreciation for the effects of PJIs on the host [17–19]. Despite the increased risk of mortality among PJI patients, we still lack the ability to directly or indirectly assign the cause of mortality due to PJIs. Therefore, the workgroup has used all-cause mortality in defining Tier 4.

Appropriate Use of the Outcome Reporting Tool

The system of tiers in the outcome reporting tool is meant to allow for a comprehensive accounting of patients in the treatment of PJIs. Therefore, each patient can only be assigned to a single tier whereby the percentage of patients among all the tiers will amount to a total of 100%. The workgroup suggests all publications reporting on the outcomes of PJI treatment include a table presenting the number of patients assigned to each tier and subgroup with certain tiers. The workgroup has recommended grouping the outcome tiers into three categories as the following: success, failure of secondary causes and failure of PJIs. Patients assigned to Tiers 1 and 2 are considered a successful outcome by representing infection control with no further reoperations. Since not all patients will experience a successful outcome or failure not due to PJIs, Tiers 3B, 3D and 4B are a failure of secondary causes not associated with PJI. Lastly, Tiers 3A, 3C, 3E, 3F and 4A are considered a failure that is directly or indirectly related to PJIs.

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QUESTION 2: Is there a minimum number of periprosthetic joint infection (PJI) procedures that surgeons should perform annually that qualifies them as experts in the management of PJIs?

RECOMMENDATION: While the optimal number of PJI cases a surgeon needs to perform annually to improve outcomes has not been established in the literature, some data suggests that surgeons that care for more PJI patients will have better results than lower volume arthroplasty surgeons. Further studies are needed to identify the minimum number of PJI cases a surgeon should perform to reduce complications and improve outcomes.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

A recent publication derived from the European Bone Joint Infection Society (EBJIS) reported on a survey based on the annual conference's delegates from all over the world [1]. It was surprising that even in this highly specific group of experts, most of them work in institutions that manage less than 50 PJIs cases per year. In a recent publication from a United Kingdom (UK) Bone Infection Unit (BIU), 362 hip PJIs were reported over a 13-year period, which were treated under the care of 10 consultant (staff) arthroplasty surgeons; this equates to three cases of hip PJI per year per staff member if the workload was evenly spread [2]. Similarly, data from a high-volume UK centre (1,000 total hip arthroplasties (THAs) per year), reported on 131 hip PJIs treated over a 13-year period by 4 surgeon (3 per year) [3]. A recent publication from another European BIU reported on 81 knee PJIs treated over a 1-year period; however, the number of surgeons treating these cases was not included [4]. Lastly, data from a high-volume United States center, reported on 205 hip PJIs over a 13-year period (16 per annum), although the number of surgeons treating the patients was not described [5]. These studies, however, failed to compare the results of higher- and lower-volume PJI surgeons.

A comprehensive systematic review failed to identify any publication that tested a surgeon's case volume as a variable for infection eradication rates or outcomes following PJIs. There are several studies, however, that demostrate that a surgeon's case volume improves outcomes in primary arthroplasty. The arthroplasty literature suggests that in primary hip arthroplasty, 35 cases per year is the optimal number above which complications reduce significantly [6,7]. A significant amount of work investigating the effect of surgeon and hospital volume on outcomes following knee arthroplasty has been performed [8,9]. Both hospital and surgeon volume were associated with decreased morbidity, mortality and length of stay. In a recent study on ouctome following unicompartmental knee arthroplasty (UKA), surgeons performing more than 30 cases per year have a significantly reduced revision rate [10]. The minimum number of cases required for improved outcome in revision work is unknown. Of interest, 80% of surgeons in the UK's national joint registry performing knee revisions undertook 10 or fewer per annum, and similarly 60% of surgeons performing hip revisions undertook ten or fewer per annum [11]. The above observations have led to the development of revision networks in order to 'centralize' the services in the UK in an effort to improve outcomes. Furthermore, data has shown that in addition to volume, the degree to which a surgeon specializes in a specific procedure may be as important as the volume of cases due to factors such as muscle memory, higher attention and faster recall [12,13]. Extrapolating these results to revision arthroplasty for PJIs, we suggest a minimum surgical volume of 25 cases per year for a surgeon to qualify as an expert in PJIs, but further studies are needed to define the optimal number. With only a few retrospective studies identifying an association between surgeon volume and outcomes in primary and revision arthroplasty, we issue a limited recommendation.

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QUESTION 3: What tools (i.e., kidney, liver, index surgery, cemented prosthesis and C-reactive protein (KLIC) score) are available to help predict successful treatment with debridement, antibiotics and implant retention (DAIR)? What is the accuracy of these tools?

RECOMMENDATION: Two prognostic scoring systems have been published and only one has been validated. While several studies exist confirming the significances of the variables utilized by the two scoring systems, the body of literature is heterogeneous and conflicted, such that general statements of their accuracy and applicability cannot be supported.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Periprosthetic joint infections (PJIs) are some of the most critical and prevalent complications following total joint arthroplasty. PJIs are associated with considerable healthcare expenses as well as patient morbidities and mortalities. Treatment strategies that have been adopted range from conservative management and antibiotic suppression to surgical treatments, such as debridement of the infected joint with or without modular component exchange, single-stage and two-stage revision arthroplasty, arthrodesis and amputation. It is yet to be determined which treatment strategy is the most effective method for treating PJIs in the patient population, but it has been shown that revision arthroplasties following PJIs fare poorly compared to revision arthroplasties following aseptic causes of prosthetic joint failures. Thus, for each patient population, it is important to identify the most appropriate treatment methods in order to prevent the recurrences of infections following treatment of PJIs. DAIR offers the advantage of physically removing most, if not all, of the infected tissue from the periprosthetic space, whereas conservative or arthroscopic treatments are less effective in removing infected tissues. DAIR also does not require the need for reoperation, making it logistically simpler than the two-stage revision arthroplasty procedure. However, indications for DAIR are generally limited to cases of acute postoperative or acute hematogenous infections not yet involving bone or causing implant loosening. There have been several studies reporting the results of DAIR that analyze factors that are predictive for treatment success or failure. However, these studies lack consistency across inclusion criteria, definitions of failure, surgical technique and timing and antibiotic regimens following surgery. This heterogeneity makes it difficult to compare results and is a likely explanation for the markedly varied risk factors and success rates seen following DAIR (16-100%) [1–3].

Two moderate-quality studies sought to construct predictive scoring tools using the most significant identified risk factors to aid in reliably assessing preoperative risk and appropriate patient selection for DAIR. Tornero et al. describes the KLIC-score to predict early failure of DAIR for acute postoperative PJIs in a retrospective regression analysis of 222 procedures (137 knees, 85 hips) [4]. The diagnosis of acute postoperative PJIs was determined using the MusculoSkeletal Infection Society (MSIS) criteria within three months of the index procedure. Early treatment failures were defined as the need for unscheduled surgery, death related to infection within 60 days of DAIR or the need for chronic suppressive antibiotic treatments. Using a logistic regression model, the authors found five independent preoperative predictors of failure. They included chronic renal failure (K- kidney), liver cirrhosis (L- liver), infection of a revision arthroplasty or arthroplasty for femoral neck fracture (I- index surgery) and cemented prosthesis and presenting C-reactive protein > 11.5mg/dL (C- cemented/CRP). The authors assigned each of these factors a point value based on the odds ratio (Table 1) and stratified the risks of failure based on the sum of these risk factors. Patients with a score of 2 or less had a failure rate of 4.5%, while patients with a score of 4 or more had a failure rate of 60%. Those with a score of at least 7 had a 100% rate of failure. Additionally, a score above 3.5 was shown to have an even balance of sensitivity (74%) and specificity (86%) in predicting early failures of DAIR [4].

TABLE 1. Scoring system of independent preoperative predictors of early failure of DAIR for PJI according to the KLIC-score

Abbreviation	Variable	Score
K	Chronic renal failure (kidney), glomerular filtration rate < 30 ml/min	2
L	Liver cirrhosis	1.5
I	Index surgery = revision surgery or indicated for femoral neck fracture	1.5
C	Cemented prosthesis	2
C	C-reactive protein > 11.5 mg/dl	2.5

K, kidney; L, liver; I, index surgery; C, cemented/CRP (reprinted with permission) [4].

The KLIC-score was later validated by Jimenez-Garrido et al. in a cohort of 30 patients with acute postoperative or acute hematogenous PJIs. They concluded that DAIR was likely to successfully treat patients with a preoperative score of < 3.5 and that DAIR was likely to fail and would not be an appropriate treatment for those scoring > 6 [5]. A subsequent external validation study by Lowik et al. retrospectively applied the KLIC-score to 386 hip and knee patients with acute, early PJI [6]. Logistical regressions showed that each point in the KLIC-score corresponds to a 1.32x increase in odds of failure. A score of 3.5 showed the optimal cut-off point for treatment, with a sensitivity of 52% and specificity of 70%. A score higher than 6 points showed a specificity of 97.9%. The KLIC-score exhibited good predictive accuracy with an area under the receiver-operating characteristic curve (0.64), but this was less than what was found in the initial study by Tornero et al. (0.84). The authors attributed this discrepancy to differences between the cohorts and in the regional epidemiology, which highlights the need for local external validation studies prior to widespread clinical adoption [6].

Buller et al. published a nomogram scoring system based on their retrospective regression analysis of 309 hip or knee PJIs treated with DAIR [7]. The authors found that independent predictors of

failure included a longer duration of symptoms of PJI prior to DAIR, elevated erythrocyte sedimentation rate (ESR) at presentation, previous PJIs, previous infections in the same joint and infections caused by *Staphylococcus aureus* (methicillin-resistant and sensitive), vancomycin-resistant *Enterococcus*, methicillin-resistant *S. epidermidis* or coagulase-negative staphylococcal species compared to other causative microorganisms. Those variables plus other patient characteristics, such as Body Mass Index, immunocompromised status, white blood cell count, hemoglobin and whether the hip or the knee is involved are used to calculate a composite score which predicts 1-, 2-, 3-, 4- and 5-year survivals of DAIR [7]. To the investigators' knowledge, this study has not been validated or utilized in subsequent citations.

With respect to the accuracy of these scoring systems, one has been validated in a 30-patient cohort and in an external validation study, but neither has been widely adopted in the literature [5,6]. However, the majority of relevant citations, despite their variability, identified predictive factors that coincide with some of the elements of the KLIC-score and the nomogram. The duration of symptoms of infection prior to DAIR, for instance, was the most widely identify factor associated with treatment outcome, with a longer duration corresponding to increased odds of failure [1,8–15]. In keeping with both systems' scoring methodologies, others have found that elevated inflammatory markers are associated with higher failure rates [8,12,16–18] and DAIR for infected knee arthroplasty has generally less favorable published results compared to their hip counterparts [2,13,19]. Performing DAIR for PJIs of revision arthroplasty [20], arthroplasty for femoral neck fracture [19] or of a cemented prosthesis [21] has also been shown to be predictive of failure in other studies. Other than the KLIC validation studies, there has been one study to identify chronic kidney disease as a predictor of DAIR failure, albeit in a cohort of exclusively gram-negative PJIs treated with DAIR [22]. No other citations, to our knowledge, have correlated liver cirrhosis to DAIR failure.

There are several other associated factors in the literature not captured by the scoring systems. Exchanging the polyethylene or modular components during debridement is consistently described as a predictor of successful treatment [20,23–25] – contemporary publications and reviews conclude that exchange of these should be standard in DAIR based on these results. Postoperative antibiotic treatments greater than 21 days, and more often at least 42 days, have also been described as positive predictors [26–28]. Appropriate antibiotic treatment varies based on causative organisms [22], but multiple citations conclude that the addition of rifampin to the antibiotic regimen is indicated for *S. aureus* infections [16,25,29–32].

The time from index surgery to PJI has had conflicting associations. Some studies show that late (i.e., acute hematogenous) infections have poorer outcomes compared to acute postoperative infections [1,8,13,24,25,33,34], while others show non-inferior results of DAIR for acute hematogenous infections as long as the duration of symptoms is short [15,34,35]. The McPherson host grading classification system, though originally described to predict successful two-stage treatment for PJI, was recently shown in total hip arthroplasty patients to predict success with DAIR [36,37]. McPherson grade A hosts failed at significantly lower rate (8%) compared to grade B (16%) and grade C (44%) hosts [37]. Preoperative anemia (hematocrit < 32.1) was recently shown to predict treatment failure after DAIR (odds ratio 6.7) [38]; anemia was included in the analysis but not found to correlate with failure in the nomogram scoring system by Buller et al. [7].

The majority of relevant citations also describe treatment rates that are pathogen-dependent. Staphylococcal species are overwhelmingly associated with high failure rates, vs. other etiologies [8,39] and most, but not all, show *S. aureus* infections to fail at significantly higher rates than other staphylococcal infections [10,26,28,40–44]. Species and antibiotic sensitivity are generally not clinically available at the time of DAIR using commonly contemporary diagnostic methods, making it impractical to include in a preoperative risk assessment system. It was not included in the KLIC-score, though the citation describes pathogen-dependent results consistent with the literature [4]. It was, however, included in the nomogram, which limits its ability to be adopted as a preoperative tool [7].

Despite the promise of these two reported scoring systems, well-controlled, high-quality studies confirming their accuracy are still lacking. The heterogeneity of the relevant literature supports both scores' methodologies, but not without some degree of conflict or inconsistency. Thus, we conclude that there exist two prognostic scoring systems: one which is a validated, preoperative assessment of risk of early failure for DAIR and one which is a non-validated nomogram of perioperative characteristics predicting 1- through 5-year survivability. Further studies adopting these scores are needed to identify those PJI patients most appropriate for treatment with DAIR.

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QUESTION 4: (A) What is the optimal follow-up plan (i.e., schedule, exam maneuvers, labs, imaging) for patients being treated for periprosthetic joint infections (PJIs)? (B) How frequently should the inflammatory biomarkers be measured after the resection arthroplasty performed as part of two-stage exchange?

RECOMMENDATION:

(A) At present, there is no consensus regarding the optimal follow-up schedule for patients being treated for PJIs and no specific research discussing this topic. In the absence of evidence, we recommend that the patients should be followed at 6 weeks postoperatively, 3 months, 6 months, 12 months, and annually thereafter, with adjustments being made based on individual circumstances. Inflammatory markers should be measured on a weekly basis after resection arthroplasty.

(B) As of now there is no study to assess the frequency with which the biomarkers need to be checked during the course of a two-stage exchange for PJIs. Most of the available studies have checked the available diagnostic battery of the tests, including serum erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) as well as synovial fluid white blood cell (WBC) count, polymorphonuclear (PMN) and leucocyte esterase (LE) at least once prior to the second stage (reimplantation). However, there is no unified protocol that provides recommendations on the timing of these tests. Future studies in this field are required to guide the orthopaedic community and help form a consensus.

LEVEL OF EVIDENCE: (A) Consensus, (B) Consensus

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

RATIONALE

The treatment of PJIs includes debridement, antibiotic and implant retention (DAIR) with or without exchange of mobile parts, single-stage exchange, two-stage exchange, long-term antibiotic suppression and salvage procedures (i.e., excision arthroplasty/arthrodesis/amputation) [1]. Due to the unavailability of specific study on this topic, all the papers on PJIs which had contents concerning the follow-up schedule were divided into groups based on specific treatments and reviewed respectively to summarize a relatively ideal follow-up timeline. The overall recommendation for follow-up visits are at 6 weeks, 3 months, 6 months, 12 months postoperatively, and yearly thereafter [2,3]. Zeller et al. [4], in their prospective cohort study on one-stage exchange arthroplasty, and Frank et al., in their multicenter randomized controlled trial that studied the effects of oral antibiotics on the reinfection rates after two-stage exchange, both have implemented the aforementioned follow-up protocol [5].

The follow-up of patients being treated for PJIs needs to be individualized based on their needs and the clinical progress. However, patients with PJIs who have undergone surgical procedures may be at higher risks of complications and issues and hence need to be followed-up more regularly. In addition, part of the clinical progress of these patients is measured using serological inflammatory markers. Thus, more regular follow-up allows the treating orthopaedic team to determine the best course of action. The latter is particularly true for patients who have undergone resection arthroplasty. These patients need to be monitored closely to determine the optimal timing of reimplantation. In addition, these patients need to be seen by the infectious disease specialists to monitor treatment response, and possibly adverse reactions, to the administered antibiotics. Although the inflammatory markers do not exactly determine the timing of reimplantation, it is important that the level of these inflammatory markers declines in the interim stage between resection and reimplantation. Additionally, determining when infection is eradicated and when reimplantation should occur remains relatively unknown which makes recommendations for follow-up also difficult.

Despite the wide array of diagnostic tests that can be used to work up a patient for PJIs, a clinical suspicion is mainly based on the initial history and physical examination [6]. They can not only help to diagnose PJI but also to identify the type of PJI encountered and assess the patient's risk factors as well as the treatment protocols.

The most common physical examinations include evaluation of the appearance of the joint, temperature of the joint skin, swelling, erythema, wound healing issues and pain with range of motion according to a systematic review of the literatures and documents regarding PJIs [6–11]. Acute infections are easier to diagnose due to the typical signs of inflammation including pain, swelling, erythema and warmth of the affected joint, accompanied by impaired wound healing postoperatively. Systemic symptoms such as fever and chills may also occur [11]. However, these typical clinical signs and symptoms may be unreliable or even entirely absent in delayed or chronic infections, especially in slow-growing organisms. The presence of a sinus tract is one of the main diagnostic criteria for PJIs [12]. Persistent pain in the artificial joint with occasional implant loosening or secondary implant failure should be considered as suspicious infections until proven otherwise [13,14].

As of now, there is no study that has specifically investigated the optimal exam maneuvers for patients being assessed for PJIs. However, a prospective study from China was performed to monitor changes in the overlying skin of knees for 12 months following unilateral total knee arthroplasties (TKAs) due to primary osteoarthritis. The authors concluded that different skin temperatures up to 12 months postoperatively may be a normal surgical response and further investigations are required to confirm if increased local skin temperatures are indeed associated with PJI [15].

The majority of studies used a follow-up plan that examines the levels of inflammatory biomarkers, but the frequency of laboratory testing is reported in very few cases. Different schedules consider ESR and CRP monitoring values every week, every two weeks, or every four weeks. However, most of the studies have monitored these biomarkers at least once after antibiotic therapy completion, prior to definitive reimplantation.

According to a study by Ghanem et al. [16], monitoring ESR and CRP before reimplantation can only poorly predict reinfections. This is true when either the absolute value at explantation or the differences between base-line values and those reported at the time of reimplantation are considered. In a study by Hoell et al. [17] they used Interleukin-6 (IL-6) as a biomarker in the follow-up plan. Their study showed that IL-6 levels prior to reimplantation are significantly higher in patients with persistent infection. However, their study was limited by sample size. Serum D-dimer has shown promising results in diagnosing PJIs. Therefore, it was suggested that this test can be used in early diagnosis of acute PJIs and determining the reimplantation timing and infection eradication [18]. However, as mentioned earlier there is no gold standard for diagnosing PJIs, and to confirm or refute the presense of infection, it is highly recommended to use a combination of tests to gather as much information as possible on the systemic response and combine it with physical exam.

Plain X-rays are the primary radiographic tool for assessing prosthetic joints. They are used to detect possible complications, including mechanical loosening, particle disease, component wear, dislocation, fracture, heterotopic ossification and infection. However, X-rays are neither sensitive (only 70%) nor specific (only 50%) [19,20]. It is usually required to compare serial images over a long period of time to be able to properly identify the changes of imaging signs such as radiolucency, osteolysis and migration of implants or spacers. Despite their low sensitivity and specificity in diagnosing PJIs, plain radiographs should be routinely performed to assess patients being treated [10,21,22].

Ultrasound has limited utility for assessing joints and is mostly used to identify the presence of significant local joint effusion [23] and to assist in the joint aspirations. CT scans and MRIs are not the optimal diagnostic tool for patients with prosthetic implants. The presence of metallic implants causes beam hardening and dephasing artifacts. However, both techniques are useful in detecting soft tissue abnormalities, such as joint effusion, sinus tracts, soft tissue abscesses, bone erosions and periprosthetic lucencies.

In terms of positron-emission tomography (PET) scans and other forms of nuclear imaging, further studies are needed because the present data regarding their accuracy is conflicting [24–26].

Bone scans have become less popular, as they have low sensitivity and specificity. The rates can be improved when a dual tracer technique, such as an indium-111-labeled leukocyte scan, is performed simultaneously with a technetium-c99m diphosphonate scan. A systematic review and meta-analysis published in 2016 has investigated the accuracy of imaging techniques in the assessment

of periprosthetic hip infections. The results showed that combined leukocyte and bone marrow scintigraphy was the most specific imaging technique for diagnosing periprosthetic hip infections. Fluorodeoxyglucose PET has an appropriate accuracy in confirming or excluding periprosthetic hip infection, but may not yet be the preferred imaging modality because of its limited availability and relatively higher cost [27].

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QUESTION 5: Is there a benefit for the engagement of a multidisciplinary team for the management of patients with periprosthetic joint infections (PJIs)?

RECOMMENDATION: The treatment of PJIs takes a multidisciplinary approach, with interactions between the orthopaedic surgeon, anesthesiologist, infectious disease specialist, medical microbiologist, plastic surgeon and ancillary service teams. It is demonstrated that centers with experience in the treatment of PJIs, or those adopting standardized protocols, have improved outcomes with lower complications. Until further research demonstrates otherwise, patients with PJIs should be cared for in centers that use a multidisciplinary approach and have experience in the management of PJIs.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Although there are a number of reports on the advantages of multidisciplinary or interdisciplinary teams (MDT/IDT) in prevention of PJIs, there is limited data on its impacts on the outcomes of PJIs. To date, no study has evaluated MDT/IDT interventions in a randomized manner and no meaningful systematic collection of data can be found.

Nevertheless, when PJIs occur, at least in specialist centers in developed countries, a number of medical, surgical and allied health

professionals are involved in management, including orthopaedics, infection disease, microbiology, outpatient parenteral antimicrobial therapy (OPAT), anesthesiology and internal medicine. Furthermore, ancillary services such as nutrition, physical therapy, pharmacy, nursing and care coordination (including physical rehabilitation, counselling, peer support, improved information) are very helpful [1].

The Oxford Bone Infection Unit (OBIU) in England and Oregon Health and Science University (OHSU) in the United States have described models of MDT/IDT care of orthopaedic infections, including PJIs, that have been developed and successfully implemented. Outputs from these centers suggest that MDT/IDT and OPAT services can improve PJI management, not only with regards to diagnosis, treatment and addressing comorbidities, but also with regards to readmissions and overall reduction of hospitalization [2,3].

A small-scale study reported five-year outcomes of a two-stage approach for infected total hip arthroplasties of a single surgeon at a tertiary center. This study prospectively highlighted the vital role of the MDT in managing 125 patients. No patients were lost to follow-up. The authors reported excellent control of infections in a series of complex patients and infections using a two-stage revision protocol supported by a multidisciplinary approach. However, there was an unexplained high rate of mortality in these patients, as 19 patients died during the study period, representing a one-year mortality of 0.8% and an overall mortality of 15.2% at five years [4].

Another study evaluated algorithm-based therapy for patients with PJIs, with emphases on establishing MDT/ IDT discussions and therapy optimizations. The study included 147 consecutive patients (with proven PJIs of the hip or knee) who were treated with a pro forma approach with an average follow-up of 29 months. Patients were treated surgically with either debridement and retention or two-stage exchange (with or without spacer). Interdisciplinary case discussions were held to adjust antibiotic and supportive therapies. The authors then evaluated the infection-free survival of all patients treated and recorded changes in therapy regime and associated complications. Although causative microorganisms were identified in 73.5% of the cases, antibiotic therapy had to be adjusted in 42% of cases based on discussions with infection specialists. A total of 71.4% and 5.4% cases were either definitely or probably free of infection, respectively. Among the study cohort, 3.4% died as a result of PJI and sepsis. Those at risk of treatment failure were cases with a septic or pre-septic status prior to the start of treatment, patients with germs rated as "difficult to treat," or polymicrobial infections, highlighting the importance of an IDT approach and its impact on success in these cases [5].

Furthermore, managing PJIs in the context of biofilms is challenging. The formation of biofilms is highly dependent on numerous factors, including the implant material, the culture media and condition, preconditioning of bacteria, the bacterial species, strain and colony morphologies (e.g., normal, small colony variants, mucoid phenotypes) and the method of evaluation. Studies on animal PJI models differ in animal types and strains, the inoculum size, and the bacterial species and strain. Therefore, animal models may not be generalized to patient management. Clinical PJI studies often lack standardization in antibiotic prophylaxis and information on the time and mechanism of bacterial colonization. Infection caused by virulent or pyogenic bacteria such as *Staphylococcus aureus* induces clinical symptoms much earlier than bacteria with low virulence.

Patients receiving orthopaedic interventions, including arthroplasty, report a negative mental outlook, functional and activity limitations, pain and loss of independence [6]. After a range of hospital admissions, individualized discharge strategies may lower the risks of readmissions and improve patients satisfactions [7]. Past medical history, clinical examination, laboratory investigations, conventional and specialized imaging, joint aspiration, microbiological and histological examinations help diagnose PJIs and are indispensable before planning and providing the appropriate therapy. Differentiation between aseptic and septic prosthetic loosening is difficult. Management of PJIs is expensive, complicated, and has a high morbidity [1]. These patients should have their definitive care by aspecialist MDT/IDT. MDT/IDT management would allow us to determine the extent of unmet needs for patients with PJIs and to evaluate existing support interventions for patients with PJIs and develop appropriate care pathways.

Based on the above search, we believe there is a gap in the available literature for systematic review or conclusion regarding this question. Further systematic studies are needed to determine the design, implementation and evaluation of MDT/IDT in the management of patients undergoing treatment for PJIs.

Literature Search

A literature search from BNI, CINAHL, Embase, HMIC and Medline was performed for ((“multidisciplinary team*” OR interdisciplinary OR MDT) AND ((prosthe* OR arthroplast*)) AND infection*). This search was conducted from inception till 10th January 2018 and 22 articles were found.

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