PART VI

FOOT AND ANKLE

Prevention

1.1. PREVENTION: TOTAL ANKLE ARTHROPLASTY-SPECIFIC

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QUESTION 1: What are the important risk factors that predispose a patient to infection after total ankle arthroplasty (TAA)?

RECOMMENDATION: There is evidence indicating that the following risk factors may predispose a patient to an infection after a TAA: inflammatory arthritis, prior ankle surgery, body mass index (BMI) < 19 and peripheral vascular disease. Meanwhile, there is conflicting evidence (which may be due to patient selection bias) indicating that the following risk factors may predispose a patient to infection after a TAA: obesity (BMI > 30), tobacco use, diabetes, duration of surgery, age < 65 years, hypothyroidism, low preoperative American Orthopaedic Foot and Ankle Society (AOFAS) hindfoot score and chronic lung disease.

LEVEL OF EVIDENCE: Limited

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

RATIONALE:

The purpose of TAA is to eliminate pain while restoring some functional range of motion. One of the dreaded complications of TAA is a periprosthetic joint infection (PJI). The reported rate of this complication ranges between 0-8.9% [1–4]. Appropriate patient selection could be facilitated by understanding the preoperative risk factors for PJI.

Inflammatory arthritis is one of the patient characteristics that have been identified by two separate studies as a risk factor for PJI. In a retrospective comparative series, Raikin et al. followed 106 patients who had undergone a TAA and identified nine patients who necessitated a return to the operating room for an irrigation and debridement and/or removal of their hardware [5]. The authors concluded that an underlying diagnosis of inflammatory arthritis was a significant risk factor leading to the complications studied. Of note, patients with inflammatory arthritis showed a 14.03-times increased risk of requiring reoperation. Althoff et al. reached a similar conclusion in a database comparative study [6]. The authors used a national insurance database to select 6,977 TAA patients and assess which factors correlated with an increased risk of PJI within the first 6 postoperative months. Several risk factors were highlighted, one of which was a diagnosis of inflammatory arthritis.

A history of prior ankle surgery has been identified as a risk factor for PJI. Patton et al. retrospectively reviewed the cases of 966 patients who had a TAA and found 29 instances of postoperative infection [7]. Prior surgery of the ankle was found to correlate with an increased risk of PJI. In a comparative cohort study, Kessler et al. evaluated 26 demographically matched patients who developed PJI, the authors concluded that prior ankle surgery increased the risk of infection [1].

Age < 65 years (odds ratio (OR) 1.61), a BMI < 19 (OR 2.67), peripheral vascular disease (OR 2.46), chronic lung disease (OR 1.51) and hypothyroidism (OR 1.32) were all determined to be a risk factor for PJI following TAA in a single study [6]. Low preoperative AOFAS hindfoot scores were also identified as a risk factor by a single study [1]. These findings, however, have not been corroborated by other publications.

There is conflicting evidence in the literature regarding the role of obesity in TAA. A single database study identified a BMI > 30 as a risk factor for developing PJI [6]. This, however, is contradicted by two separate retrospective comparative series. Schipper et al. assessed the outcomes between 49 obese patients and 48 non-obese patients following TAA [8]. While the authors noted that there was decreased survivorship of the implant in the obese patient population, there was no increased risk of infection. Similar findings were noted in a large case series comparing patient-related factors between TAAs that developed infection and those that did not [7].

Whether tobacco use is a risk factor for PJI is not clear based on the current literature. The database publication by Althoff et al. concluded that smoking increases the risk of a PJI (OR 1.59) [6]. Lampley et al. compared the postoperative outcomes between nonsmokers (n = 359), former smokers (n = 249) and current smokers (n = 34) [9]. The authors concluded that while the active smokers had an increased rate of PJI, this did not reach statistical significance. Patton et al. however, concluded in their large case series that there was no association between tobacco use and postoperative infection following TAA [7].

The current literature is divided on the issue of whether diabetes is considered a risk factor for PJI [6–8,10]. The publications by Althoff et al. [6] and Patton et al. [7] both conclude that diabetic patients are at increased risk of infection. Further, Schipper et al. reached a similar conclusion that diabetes was an independent risk factor [9]. However, Gross et al. assessed the complication rate between 50 diabetic patients and a control group and concluded that diabetes did not increase the risk of infection [10]. Additionally, the length of the operative procedure is a risk factor that has shown some variance in the literature. Kessler et al. reported that the duration of the surgery was significantly longer (119 minutes) in the infected group, compared to the age and sex-matched control group (84 minutes) [1]. In contrast, Patton et al. found no difference in operative times between patients who developed a PJI and those who did not [7].

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QUESTION 2: Does intra-articular injection of the ankle with corticosteroids increase the risk of subsequent periprosthetic joint infection (PJI) following total ankle arthroplasty (TAA)? If so, how long after a prior intra-articular injection can TAA be safely performed?

RECOMMENDATION: Every intra-articular injection of the ankle is an invasive procedure associated with potential healthcare-associated infections, including periprosthetic joint infection (PJI) following TAA. Based on the limited current literature, the ideal timing for elective TAA after corticosteroid injection for the symptomatic native ankle joint is unknown. The consensus workgroup recommends that at least three months pass after corticosteroid injection and prior to performing TAA.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 92%, Disagree: 8%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

Intra-articular steroid injections may transiently relieve the pain of osteoarthritis of the ankle and are widely used for its treatment. At the same time, every injection is an invasive procedure and might be associated with health-care-associated infections, including PJI following TAA. Seror et al. noted that the risk of septic arthritis after an intra-articular steroid injection is 1 in 70,000 [1]. For native ankle joints, one study found a 3.9% infection risk when using intraoperative steroids versus a 1.8% infection risk when performing arthroscopy without steroids [2]. However, this study was not related to TAA, and many other studies in native ankle joint arthritis deny a relationship with steroid injections.

The available literature investigating the effect of intra-articular corticosteroid injections on postoperative PJI are all in hip and knee arthroplasty patients. Some studies find no relationship between corticosteroid injections and infection [3–6], while others find an increased risk of deep infection following intra-articular injection [7–11]. Studies that find a positive correlation also suggest that timing may be an important factor, and that injections more closely preceding surgery may lead to an even higher risk of infection.

Unfortunately, there are no published data in regards to the risk of PJI after steroid injection in the setting of TAA. The data from hip and knee arthroplasty may not be applicable to TAA, and further studies are warranted.

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QUESTION 3: Should routine methicillin-resistant *Staphylococcus aureus* (*S. aureus*), or MRSA, screening be in place prior to total ankle arthroplasty (TAA)?

RECOMMENDATION: Unknown. The role of screening for MRSA and decolonization prior to TAA remains unclear. Further data is needed to support this practice in TAA, which can be costly and logistically difficult to implement.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

There is growing concern about the increase of postoperative infections due to antibiotic-resistant organisms [1], and this is particularly important in orthopaedic surgery where the increasing incidence of antibiotic-resistant *Staphylococci* threatens the outcome of implant-related procedures. The complication rate and cost of periprosthetic joint infection (PJI) associated with MRSA is considerably higher compared to those associated with methicillin-sensitive *Staphylococcus aureus* (MSSA) [2]. Patients receiving orthopaedic implants are most vulnerable, given the potential for biofilm formation and long-term morbidity [3].

Furthermore, the prevalence of surgical site infections (SSIs) as a result of MRSA has increased over the last few years. Between 1992 and 2003, the prevalence of MRSA increased from 32% to 64% of all isolated nosocomial pathogens found on patients in hospital intensive care units (ICUs), representing a 3.1% increase in MRSA prevalence per year [4].

The last two decades have seen an increase in community-acquired MRSA (CA-MRSA), a subpopulation of MRSA with unique antibiotic resistance properties, high virulence characteristics and pathogenic capability. This subset of MRSA tends to affect young and otherwise healthy patients [5–7].

Several screening strategies have been studied in terms of their cost-effectiveness [8,9]. As the *S. aureus* strain isolated from SSIs commonly matches (in up to 85% of cases) the *S. aureus* strains sampled from the noses of colonized patients, nasal swabs emerge as a potentially cost-effective screening option [10–12].

However, the evidence is not conclusive regarding an association between rapid screening and the acquisition rate for MRSA or risk of MRSA-induced SSIs. However, in the setting of a positive result, it allows for the implementation of a decolonization protocol that is indeed effective in significantly reducing the rate of SSIs caused by MRSA [7].

A recently published, large multicenter prospective cohort trial by Schweizer et al. involving > 40,000 unique operations examined the effect of the introduction of a standardized preoperative *S. aureus* screening and decolonization program on deep *S. aureus* SSIs in cardiac surgery and hip and knee arthroplasties performed at 20 hospitals [13]. The authors reported that the hip and knee arthroplasty cohort demonstrated a significant reduction in postoperative rates of deep infection with *S. aureus* following the introduction of the screening and decolonization program.

Numerous studies have demonstrated that the most common pathogens in SSIs following total hip arthroplasty/total knee arthroplasty (THA/TKA) are MSSA and MRSA. Additionally, many of these studies have demonstrated that positive colonization correlates with increased SSIs and multiple studies have demonstrated the benefit of treating patients who test positive on preoperative screening. When assessing the cost-effectiveness of screening and decolonization, multiple studies have shown potential to substantially reduce the cost of THA/TKA by decreasing the rate of SSIs. Lastly, recent studies have demonstrated cost-effectiveness in universal decolonization programs with or without the inclusion of preoperative *S. aureus* screening. The latter has become a reality as numerous non-antibiotic agents have been introduced.

In the absence of concrete evidence supporting MRSA screening and decolonization in patients undergoing TAA, perhaps consideration should be given to universal decolonization of these patients using one of these non-antibiotic agents.

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QUESTION 4: What preoperative optimization should be implemented to reduce the risk of surgical site infection/periprosthetic joint infection (SSI/PJI) in patients undergoing total ankle arthroplasty (TAA)?

RECOMMENDATION: We recommend that patients awaiting TAA be optimized prior to surgery by implementing skin cleansing, nutritional status enhancement, glycemic control, body mass index (BMI) optimization, smoking cessation, and management of immune-modulating comorbidities.

At the time of surgery, there is strong evidence that optimal preparation of the surgical site with an alcohol-containing agent, weight-based and timely administration of antibiotic prophylaxis, and reducing operating room traffic should also be put in place.

LEVEL OF EVIDENCE: Moderate

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

RESPONSE

PJIs complicating total joint arthroplasty (TJA) are potentially catastrophic events to patients and immense financial burden to the healthcare system [1,2]. These events can occur intraoperatively, immediately postoperatively or as a late complication via direct or hematogenous spread of pathogens to the prosthetic joint. The prevention of this potentially serious complication should always be a priority, and this is best achieved by the implementation of proper preventive strategies. Though preoperative optimization prior to TAA is limited in the literature. We recommend utilizing similar methods proven to prevent infection after total knee and hip arthroplasty.

In an attempt to decrease SSIs caused by *Staphylococcus aureus* (*S. aureus*), or MRSA, Alexander et al. recommended the use of chlorhexidine footbaths in patients with nasal colonization of *S. aureus* beginning five days prior to their foot and ankle surgery in addition to standard operative disinfection protocols [3]. Colling et al. demonstrated that a preoperative antiseptic shower and bath policy was associated with a significant decrease in *S. aureus* and MRSA SSI [4]. Despite being a valid option in preventing *S. aureus* and MRSA infections, this shower and bath policy failed to achieve a decrease in the total incidence of SSI. Prior to the procedure, prophylactic antibiotics such as cefazolin can be administered to patients, as this is considered an essential part of the foundation of SSI prevention due to its long-accepted reduction of infection in orthopaedic procedures and a current recommendation from the American Academy of Orthopaedic Surgeons [5–7]. Interestingly, in their retrospective study comparing the use of antibiotic prophylaxis either 15-60 minutes or less than 15 minutes prior to foot and ankle surgeries, Tantigate et al. found that the timing of intravenous antibiotic prophylaxis did not play a significant role in the risk of developing SSI [5].

In addition to external preventative measures, optimizing the nutritional status of patients undergoing TAA to optimize the immune system is important. Several studies on infections following orthopaedic procedures have demonstrated that a lymphocyte count below 1,500 cells/mL, an albumin level below 3.5 g/dL, a zinc level below 5 mg/dL, and a transferrin level below 200 mg/dL have been associated with increased risks of infection and delayed wound healing [8–12]. Therefore, nutritional parameters should be measured in those suspected of being malnourished and the abnormal parameters corrected prior to elective arthroplasty.

The optimization of medical comorbidities should also be considered an essential part of the preoperative protocol aimed at reducing PJI following TAA. Marchant et al. reported that the current glycemic control of patients with diabetes mellitus (DM) is more important toward the risk of infection following TJA rather than the diagnosis of DM itself, as the risk of infection of diabetic patients with controlled glucose levels was the same as patients without DM [13]. In their study on total hip and knee arthroplasties, Mraovic et al. further concluded that blood glucose levels immediately prior to and after surgery were significantly correlated with subsequent infection risk. These authors reported that non-DM patients with blood glucose levels greater than 140 mg/dL on the morning following surgery had a three-fold increase in infection risk [14]. Therefore, proper glycemic control in all patients should be performed in order to decrease the risk of SSI and PJI.

As obesity has been consistently shown to be associated with SSI risk in total hip and knee arthroplasties, especially BMI > 30 kg/m^2, weight reduction strategies leading up to surgery as well as dose-based antibiotic prophylaxis immediately prior to surgery in obese patients should be performed [1,15,16].

Certain other comorbidities are also highly related to an increased risk of infection in TJA due to decreased patient immunity, and these should be taken into consideration prior to surgery [1]. In their investigation into patient-related risk factors for PJI following TAA, Althoff et al. reported that, in addition to DM and obesity, a BMI < 19 kg/m^2, tobacco use, inflammatory arthritis, peripheral vascular disease, chronic lung disease and hypothyroidism were independent risk factors for PJI development following TAA [17]. Therefore, smoking cessation and optimization of these other aforementioned medical comorbidities should be performed prior to surgery. In their discussion of infection reduction following TJA, Matar et al. recommends this optimization of patient health through a preoperative evaluation by an internal medicine consultant or cardiologist, who subsequently follows the patient throughout their hospital course and postoperative period [18].

In the period immediately prior to surgery and within the operating room, we recommend utilizing the specific measures reported by Illingworth et al. and Matar et al. regarding infection minimization in TJA [1,18]. Optimization through the assessment of the skin around the ankle for any irregularities, surgical site skin decontamination through alcohol and betadine solutions, surgical site shaving, planning of surgical incision path, and appropriate draping with plastic adhesive, iodine-impregnated drapes should be considered in order to reduce PJI following TAA [18,19]. In addition, implementation of intraoperative measures, such as reducing foot traffic, having an operating room with an efficient ventilation system to reduce aerosolized particles and performing the surgery in an expeditious manner, are all proven to reduce the risk for subsequent SSI/PJI [18, 20–25].

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QUESTION 5: What prophylactic antibiotic (type, dose and route of administration) should be administered perioperatively for patients undergoing total ankle arthroplasty (TAA)?

RECOMMENDATION: The administration of prophylactic antibiotics before TAA potentially reduces the incidence of surgical site infection (SSI) and/or periprosthetic joint infection (PJI). Weight-based (of at least 2 gm) Cefazolin administered intravenously within 60 minutes prior to the procedure can be an adequate choice for antibiotic prophylaxis.

If the patient has a beta-lactam anaphylaxis, we recommend an appropriate alternative antibiotic effective against *Staphylococcus*.

It is unclear whether prophylaxis should be given as a single dose or as multiple doses.

LEVEL OF EVIDENCE: Strong

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

RATIONALE

Published studies report a rate of PJI after TAA that ranges from 2 to 8.6%, exceeding the risk of infection following knee and total hip replacements [1]. Likewise, the incidence of SSI following foot and ankle elective surgeries (2-4.5%) is higher than other orthopaedic procedures [2].

Most expert panels consider it appropriate for antimicrobial prophylaxis to be routinely utilized in surgeries involving prosthetic joints [3–8]. Unfortunately, no high level evidence is available to corroborate its indication specifically in TAA [9,10].

Gram-positive cocci are the most prevalent pathogens in SSI and PJI in foot and ankle surgeries [1,5,11]. Cefazolin is the more widely used antibiotic for standard prophylaxis in orthopaedic surgeries, due to its effective and rapid bone and soft tissue penetration, excellent gram-positive coverage and its long half-life [12,13]. One to 2 grams of Cefazolin administered intravenously is the standard dosage recommended in most guidelines, although some experts suggest increasing the dose to 3 grams if the patient weighs more than 120 kilograms [3,4,7,12]. In patients with a history of severe beta-lactam allergy, who cannot receive cephalosporins, vancomycin or clindamycin are adequate alternatives [3,4,12].

Some studies show reduced SSI rates associated with methicillin-resistant *Staphylococcus aureus* (MRSA) screening and decolonization protocols in elective orthopaedic procedures, but there is no specific data in foot and ankle surgeries or TAA [14,15]. Most experts

recommend performing these procedures on a case-by-case basis, taking into account the history of colonization and the presence of risk factors for MRSA [10,15].

Most guidelines advocate for the administration of prophylactic antibiotics within 60 minutes prior to surgery [3,4,6,7,10]. Studies that assessed patterns of antibiotic bone penetration in prosthetic joint replacements report that effective serum levels of Cefazolin persisted for over eight hours after intravenous administration, achieving peak concentration in bone tissue 40 minutes after the dose [13]. Antibiotic administration 15 minutes prior to incision has not proven to be better than 15-60 minutes before the procedure [2]. Experts advise redosing if procedure time exceeds one to two times the half-life of the antibiotic (1.5-two hours in case of Cefazolin) [3,4,6]. There is conflicting evidence for the need to continue prophylaxis postoperatively, but it is clear that there is no benefit in extending the administration of antibiotics beyond 24 hours after the surgical procedure [4–7,10]. If a proximal tourniquet is used, the antimicrobial should be completely infused before inflation [10,13].

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QUESTION 6: What is the optimal management of patients with prior septic arthritis of the ankle who are undergoing total ankle arthroplasty (TAA)?

RECOMMENDATION: There is a paucity of data regarding TAA in patients with prior infection involving the ankle, whether it be septic arthritis, osteomyelitis or infection of the surrounding soft tissues.

We recommend that patients with prior infections in the affected ankle be worked up for infection, including a thorough history and physical examination, as well as ordering serological tests and possible aspiration of the joint. During ankle arthroplasty in patients with prior infection, antibiotics should be added to the cement (if used), and the joint should be thoroughly cleansed. Intraoperative cultures of bone and soft tissue should also be obtained.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

TAA has been used with increasing frequency for the treatment of end-stage arthritis of the ankle. The rate of periprosthetic joint infection (PJI) of the ankle varies in the literature. When it occurs, it can have devastating consequences. There is a paucity of literature regarding the work-up, management and outcomes of PJI in TAA.

With regards to total ankle arthroplasty in patients with a history of infection involving the ankle, only one study in the literature was identified and was a level IV case series. A history of infection in or around the ankle was traditionally seen as a relative, if not absolute, contraindication to TAA [1,2]. However, until 2015, there were no studies on the matter in the foot and ankle literature.

Shi et al. retrospectively identified 22 patients over a 7-year period who underwent TAA who had a history of septic arthritis of the ankle or periarticular osteomyelitis [3]. The preoperative workup for these patients differed based on clinical suspicion and the treating surgeon's preferences. At the very least, all patients had preoperative blood work in the form of a complete blood count (CBC), erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels. The decision to perform a preoperative joint aspiration or send intraoperative frozen sections or tissue samples for culture was surgeon-dependent.

At a mean follow-up of 29.3 (range, 11.4 to 83.8) months, there were no PJIs, evidence of radiographic loosening or need for revision of the components. The TAA was performed at an average of 8.8 (range, 0 to 44) years after the diagnosis of infection in or around the ankle. Three patients (14%) had delayed wound healing, and three others (14%) underwent subsequent procedures, which were not for the infection and did not involve revision of any of the ankle arthro-

plasty components. The authors of this study concluded that TAA may be a viable option for patients with a history of infection of the ankle [3].

While this study does demonstrate the potential for infection-free survival of a TAA in patients with a history of infection in or around the ankle, the follow-up of the cohort is too short to allow conclusive recommendations to be made regarding this patient population. Therefore, further studies on the topic are needed. In the interim, we recommend that all patients with infection in or around an ankle that is being considered for TAA be worked up for infection prior to the elective arthroplasty. During the arthroplasty, additional measures should be implemented to reduce the risk of subsequent SSI/PJI.

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Authors: Jonathan Kaplan, John M. Embil

QUESTION 7: During draping for total ankle arthroplasty (TAA), should the foot be prepped into the surgical field or be covered?

RECOMMENDATION: There is insufficient data demonstrating any advantage or disadvantage to covering the toes during TAA.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Multiple studies have shown increased rates of bacterial colonization in the toes after skin preparation [1–4]. Zacharias et al. reported on the pre-procedural cultures in 12 patients who underwent lower extremity orthopaedic surgery not involving the foot [4]. The authors performed pre-procedural toe cultures, prepared the extremity with povidone-iodine and followed with coverage of the toes with a self-adherent wrap. The authors found a 75% rate of positive pre-procedural and aerobic cultures, concluding that there is some benefit to applying sterile draping to the toes in order to minimize the risk of infection. However, the major weaknesses of the latter study are the small sample size (n = 12), lack of a control group, preparation of the surgical site being done by an operating room nurse not aware of the study and the use of povidone-iodine.

In another study, Brooks et al. demonstrated that there was a significantly lower rate of bacterial recolonization in patients who underwent a standard antiseptic technique in combination with sliding a gauze swab soaked in topical antiseptic multiple times between the toes compared to standard antiseptic technique alone [1].

Hort and DeOrio designed a study that assessed the amount of residual bacterial contamination after surgical preparation of the foot and ankle with or without the use of alcohol [2]. In this study, the 49 patients were randomly assigned to either a standard preparation with chlorhexidine gluconate home scrubs and preoperative povidone-iodine or a standard preoperative preparation with the addition of 70% alcohol. While there was a trend towards significance, the authors found no significant difference in colonization rates with or without the use of alcohol. However, they found high rates of residual colonization (35% in the standard surgical group and 57% in standard preparation plus alcohol). Subsequently, the authors' conclusions included the recommendation of covering the toes during hindfoot and ankle surgery. No patient had any clinical evidence of infection or wound problems. It should be noted, however, that this study did not specifically compare patients with their toes uncovered or covered.

However, despite the presence of studies recommending covering the toes to decrease the risk of contamination in lower extremity surgeries, there are limited studies assessing the rates of infection with the toes covered versus uncovered. Goucher et al. performed a prospective, randomized study to assess the effect of covering the toes during hindfoot and ankle surgery [5]. In this study, they performed three sets of cultures (before skin prep, immediately after skin prep and after the conclusion of the surgery) from the foot and toes from one group of 20 patients with their toes covered and a second group of 20 patients with their toes uncovered. Of 40 patients, only two postoperative cultures were positive, and neither of these patients showed any signs of postoperative infection. Additionally, while seven patients showed signs of superficial infection (erythema, superficial dehiscence or suture abscess), there was no difference between the two groups. Therefore, the authors concluded that there were no benefits in covering the toes in hindfoot and ankle surgery.

Recently, the order of skin preparation has also been investigated. Hunter et al. performed a prospective, randomized control study to assess the proper order of skin preparation of foot and ankle orthopaedic surgeries [6]. The authors found that there were lower rates of positive post-procedural cultures in patients undergoing preparation with isopropyl alcohol followed by chlorhexidine compared to patients undergoing preparation with chlorhexidine followed by isopropyl alcohol. However, no assessment was performed comparing coverage versus non-coverage of the toes during the procedure.

Although inconclusive, there is ample evidence of persistence of bacterial colonization irrespective of skin preparation technique of the foot. Consideration should be given to covering the toes to limit the risk of contamination of the surgical site and the potential for subsequent infection.

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Author: Jens Richter

QUESTION 8: Should antibiotic-impregnated cement be used during primary total ankle arthroplasty (TAA)?

RECOMMENDATION: Unknown. There is insufficient evidence for the routine use of antibiotic-impregnated cement during primary TAA.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

The main sources for this systematic review were the Medline, Embase, CINAHL and Cochrane CENTRAL databases, beginning with the first citation of ankle arthroplasty in July 2003, the 2016 Swedish Ankle Registry [1] and the 2016 New Zealand Joint Report [2].

In their report on the New Zealand Joint Registry, Rothwell et al. reported on 1,261 TARs from January 2000 to December 2015. Cement fixation was used only in 13 tibial components and in seven talar components. Antibiotic-impregnated cement was used seven times for tibial component fixation and three times for the talus component fixation. However, there was no statistical evaluation in this registry for the item periprosthetic joint infection (PJI) according to the type of cement used.

Considerable research is available related to PJI and antibiotic-impregnated cement for total knee arthroplasty (TKA) procedures. Gutowski et al. stated in their study that the absolute rate of infection increased when antibiotic-loaded cement was used in TKA, although this was less when compared to infection rates after use of plain cement [3]. In 2016, Schiavone et al. performed a systematic review determining the effectiveness of utilizing antimicrobials and the safety of antibiotic-loaded bone cement in primary TKA [4]. The authors concluded that there was no significant difference in the rate of deep or superficial surgical site infection in patients receiving antibiotic-impregnated cement in primary TKA compared with those receiving plain cement.

Based on the lack of proven efficacy for antibiotic-impregnated cement in the prevention of PJI in the TKA literature and the lack of research into antibiotic-impregnated cement in TAA, we cannot provide a recommendation for or against the routine use of antibiotic-impregnated cement during TAA. However, this point may be of limited current importance anyway, as the majority of modern generation TAA are cementless in design.

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1.2. PREVENTION: NON-TOTAL ANKLE ARTHROPLASTY-SPECIFIC

Authors: Gaston Slullitel, Yasuhito Tanaka, Ryan Rogero, Valeria Lopez, Eiichiro Iwata, Yusuke Yamamoto

QUESTION 1: What are the benefits and risks associated with the use of vancomycin powder in the wound during total ankle arthroplasty (TAA) or other foot and ankle procedures?

RECOMMENDATION: Though one study supporting topically-applied vancomycin has shown it to reduce the rate of deep infection in diabetic patients undergoing foot and ankle surgery, there is insufficient evidence to show benefits or to show any risks associated with the use of vancomycin powder during TAA or other foot and ankle procedures in a general population.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

The effects of the use of vancomycin powder in foot and ankle surgery are ill-defined. Wukich et al. evaluated the use of vancomycin powder exclusively in foot and ankle procedures, though this was performed in a population composed solely of patients with diabetes mellitus [1]. The authors concluded that odds of surgical site infections (SSIs) (73% decrease) and deep infections (80% decrease) were significantly reduced in diabetic patients who underwent reconstructive surgery of a foot and/or ankle deformity or trauma and received topically-applied vancomycin when compared with a group of patients who did not receive topically-applied vancomycin. The rate of superficial infections did not differ significantly between the two groups. Based on this retrospective controlled study, the authors concluded that foot and ankle surgeons may consider topically applying 500 to 1,000 mg of vancomycin powder prior to skin closure in patients who are not allergic to vancomycin. To our knowledge, no others studies have evaluated the use of vancomycin powder exclusively in foot and ankle surgery.

The effectiveness of vancomycin powder has been documented more extensively in other orthopaedic subspecialties than foot and ankle [2–6]. A systematic literature review by Kanj et al. showed local vancomycin-impregnated cement and powder to be associated with lower infection rates while also being safe and effective in clean orthopaedic surgery [2]. The authors especially recommended utilizing local vancomycin in spine surgery, in which patients without local antibiotic prophylaxis were more than four times more likely to experience a deep postoperative wound infection. Evaniew et al. concluded through their meta-analysis that there is a lack of high-quality evidence to inform the use of intrawound vancomycin in spine surgery [3]. Xie et al. found from their meta-analysis on intrawound vancomycin in spinal surgery that the odds of developing postsurgical wound infection without prophylactic local vancomycin use were 2.83-fold higher than the odds of experiencing wound infection with the use of intrawound vancomycin [4]. Furthermore, a retrospective review performed by Singh et al. that assessed the efficacy of intraoperative vancomycin powder administration on preventing deep SSI in high-energy lower extremity trauma (including tibial plateau fractures and pilon fractures) found that the rate of deep SSI between the groups was not statistically significantly different [7].

Concerns have been raised about the potential risks of the local use of vancomycin, including selection for gram-negative and multi-drug-resistant bacteria, increased local tissue irritation, hypersensitivity or anaphylaxis, impaired renal function, and increased seroma formation [8]. However, these adverse effects are mostly hypothetical and have not been reported in the literature, though a case of circulatory collapse due to topical vancomycin application during spine surgery was identified [9].

Although vancomycin powder appears to be effective at decreasing postoperative infections in spine surgery according to some studies, a large void remains in the evidence for other orthopaedic subspecialties, especially foot and ankle. Randomized controlled trials, particularly within the fields of arthroplasty and trauma, are needed to determine the efficacy of local vancomycin powder for infection reduction. In this scenario, a phase III prospective randomized clinical trial is being conducted among high-risk tibial fracture patients to assess the efficacy of locally administered vancomycin powder in the prevention of SSI after fracture surgery [10], which may bring increased clarity to this matter.

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QUESTION 2: Is there a role for the use of dilute povidone-iodine (betadine) irrigation or other antiseptic irrigation solutions during total ankle arthroplasty (TAA) or other foot and ankle procedures?

RECOMMENDATION: With regards to TAA, there is a lack of evidence to recommend for or against the use of betadine solution.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

In 2016, the World Health Organization (WHO) published guidelines for the prevention of surgical site infections (SSIs) [1]. Based upon a review of 17 randomized controlled trials, there is moderate quality evidence that alcohol-based antiseptic solutions for preparation of the surgical site decrease the risk of SSIs in comparison to aqueous solutions. A low quality of evidence showed decreased SSI risk with alcohol-based chlorhexidine gluconate compared to alcohol-based betadine. While alcohol may be concerning for persons from certain religions, the WHO guideline highlights the statement issued in 2002 by the Muslim Scholars Board of the Muslim World League. According to the Board, medicines containing alcohol may be used as an external cleaner. With the use of alcohol-based agents, care must be taken to allow them to dry completely, as operating rooms fires have been reported. According to the Centers for Disease Control and Prevention (CDC), skin preparation with an alcohol-based antiseptic solution should be completed prior to surgery, to reduce the risk of SSI [2].

A systematic review and meta-analysis of combination chlorhexidine gluconate (CHG) and betadine implicated the utility of these agents, despite the low quality of the evidence. A major limitation of many of these studies, however, was the use of bacterial colonization as an endpoint rather than the development of a true SSI [3].

Privitera et al. recently provided a meta-analysis updating and clarifying issues from prior meta-analyses which had not clearly distinguished among studies using alcohol and aqueous-based products. In the updated meta-analysis, there was subgroup analysis showing decreased colonization rates with chlorhexidine, but there was not a statistically significant difference in SSI due to the low numbers of SSI [4].

Although the use of antiseptic agents for skin preparation is necessary for bioburden reduction and prevention of infection, there is minimal data available regarding the role of antiseptic irrigation solutions during TAA. The use of antiseptic agents for irrigation is often performed in the setting of periprosthetic joint infections (PJI) of the hip and the knee, although the utility in total ankle replacements is unknown.

Randomized controlled studies have evaluated the use of various irrigates in open fracture wounds, noting that normal saline was more efficacious and as effective at decreasing infection in comparison to castile soap and bacitracin solution, respectively [5,6]. Chlorhexidine solutions have been evaluated in an in vitro model as being beneficial to decreasing the biofilm load, particularly at concentrations above 2%. However, of importance is that concentrations as low as 0.02% CHG have shown to lead to fibroblast toxicity [7,8]. Dilute betadine may be advantageous in this regard, as it has minimal cellular toxicity at low concentrations and excellent efficacy for prevention of infection [9].

Based on the available data, the CDC has recommended that strong consideration should be given to the use of dilute betadine during all surgical procedures. Although no data in TAA exists, extrapolating the recommendations of the CDC to TAA appears to be reasonable as dilute betadine is inexpensive, efficacious and carries little-to-no cell toxicity.

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QUESTION 3: Does revascularization prior to foot and ankle surgery reduce the incidence of surgical site infection (SSI)?

RECOMMENDATION: Several studies support the effect of peripheral vascular disease (PVD) on wound healing and SSI. Despite this, there have been no specific studies proving the beneficial effect of revascularization on SSI prior to surgical intervention in the setting of traumatic or elective foot and ankle surgery. The majority of studies on revascularization are in the setting of diabetic foot infection or established ischemia.

We recommend that in the presence of an inadequate vascularization in the foot and ankle, vascular optimization should be undertaken prior to elective surgery.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Oxygenation of soft tissues is a critical component of wound healing, with wound tissue oxygen tension having a direct correlation with the risk of postoperative wound infection [1].

Diabetes mellitus (DM) and its complications, such as PVD, have proven to be risk factors for increased infection and complication rates after surgery for ankle fractures [2–4]. A large cohort study of

over 57,000 patients found that PVD alone was a strong risk factor for the development of complications after ankle fracture fixation, with the rate of infection increased from 1.44% to 6.87% in the presence of PVD [2].

Diabetes and PVD are associated with increased complications in other forms of foot and ankle surgery, as well [5]. PVD is a proven risk factor for infection after arthrodesis procedures of the foot and ankle and is an independent risk factor for periprosthetic joint infection (PJI) following total ankle arthroplasty [6,7].

Clinical guidelines for the management of diabetic foot disorders suggest a thorough assessment for vascular risk factors prior to surgery [8]. PVD and poor oxygen delivery to tissues are associated with poor wound healing in these patients and should thus be identified [9,10]. Angiography should also be performed when appropriate to assess the potential for revascularization [8], as this intervention has shown to improve the level of amputation and tissue loss in this group of patients [11–13]. Furthermore, Faglia et al. demonstrated revascularization in diabetic patients with critical limb ischemia to lead to a low rate of early amputation [14].

Aust et al. reported that combining revascularization with surgical intervention results in improved wound perfusion and healing of chronic wounds [15]. Revascularization prior to surgery can even allow for successful primary closure of some chronic wounds, according to Barshes et al. [16]. Furthermore, two groups have reported that if primary closure is not viable, then revascularization can be completed in the setting of free tissue for chronic wounds [17,18].

Transmetatarsal amputation can be an effective method of limb salvage in the ischemic or infected diabetic foot, and the rates of wound healing and limb salvage have demonstrated to be improved in conjunction with revascularization [19,20]. Additionally, it is important to understand that the timing of revascularization prior to surgery has not been shown to influence outcomes [21,22]. This would suggest that revascularization prior to diabetic foot surgery is not essential but beneficial when performing revascularization close to foot and ankle surgery in the diabetic patients.

There is little literature related to the effect of revascularization in preventing SSI in foot and ankle surgery. While the presence of PVD is known to increase the risk of SSI/PJI in patients undergoing foot and ankle procedures, no specific study demonstrates revascularization of the foot and ankle obviates this increased risk.

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QUESTION 4: Are prophylactic perioperative antibiotics required for isolated forefoot procedures, such as hammertoes?

RECOMMENDATION: Though limited clinical data exists, the administration of perioperative antibiotics is not required for isolated forefoot procedures in the absence of any risk factors, such as immunodeficiency or diabetes mellitus.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 67%, Disagree: 25%, Abstain: 8% (Super Majority, Weak Consensus)

RATIONALE

One high-quality and one moderate-quality prospective randomized control study have demonstrated that there is no significantly different rate of infection in patients who received perioperative antibiotics compared to those who did not receive antibiotics [1,2]. There are also multiple other low-quality studies to support this finding.

A prospective randomized controlled trial of 100 adults undergoing toe fusion with Kirschner wires (K-wires) revealed no significant difference in the infection rate between the group that received prophylactic antibiotics (6.2%) versus the group that did not receive antibiotics (1.9%) [1]. Additionally, a recent multicenter, double-blinded, randomized clinical trial of 500 patients undergoing removal of orthopaedic implants from the lower extremity in the Netherlands showed no significant difference between the group that received a single preoperative dose of intravenous cefazolin (13.2%) when compared to the group that received saline (14.9%) [2].

In their retrospective analysis of 555 patients who underwent elective foot and ankle surgeries, Zgonis et al. reported a 1.9% rate of infection in those who received preoperative antibiotics, compared to a 1.4% rate in patients who did not receive preoperative antibiotics [3]. The authors concluded that prophylactic intravenous antibiotic use in routine elective foot and ankle surgery is not warranted.

Based on a systematic review of the literature, the American College of Foot and Ankle Surgeons has made a recommendation that although there is little to no empiric evidence to support administrating prophylactic antibiotics in elective foot and ankle surgical procedures, antibiotics should be considered [4,5]. They concluded that there is a relative divide between empirical science and common practice. Despite the absence of evidence to support the use of prophylactic antibiotics, it is nevertheless widely used and is a requirement of most hospital systems in order to satisfy quality measures. They justified the practice as being an intervention without significant risk. However, the cost to the healthcare system or the potential for the emergence of resistant organisms was not considered in their 2015 and 2017 statements.

In a survey emailed to all active and candidate members of the American Orthopaedic Foot and Ankle Society, Ruta et al. reported that the majority (75%) of orthopaedic foot and ankle surgeons use prophylactic postoperative oral antibiotics [6]. Most surgeons (69%) prescribed antibiotics to fewer than 25% of patients, although 16% of surgeons prescribed for all elective cases. The finding of the survey was that there was no significant difference in surgical site infection rate among the patients of surgeons who prescribed antibiotics versus those who did not. Another national survey study showed that 25% of attending physicians at foot and ankle fellowships in the United States would administer perioperative antibiotics for foot and surgeries that require K-wire fixation [7].

There is no scientific evidence to support the administration of prophylactic intravenous antibiotics in elective forefoot surgeries. However, even with the lack of high-quality clinical studies, the administration of perioperative antibiotics as a quality measure for most hospital systems and being considered a common practice have led surgeons to administer perioperative antibiotics for forefoot surgeries.

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Diagnosis

2.1. DIAGNOSIS: TOTAL ANKLE ARTHROPLASTY-SPECIFIC

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QUESTION 1: What is the definition of acute and chronic periprosthetic joint infection (PJI) of total ankle arthroplasty (TAA)?

RECOMMENDATION: There is a paucity of data for defining acute or chronic PJI following TAA in the literature. Any discussion of PJI after ankle replacement is entirely reliant on the literature surrounding knee and hip arthroplasty.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE:

PJI after TAA is an unfortunate and serious complication that bears significant consequences to the patient and impediments to the natural history of ankle replacement, often prompting revision arthroplasty, conversion to arthrodesis or potentially below-the-knee amputation. While the practice of TAA has gained popularity in recent years [1], there is a paucity of data describing wound complications and acute or chronic PJI of TAA. The review of the current literature fails to identify a specific set of accepted criteria for defining an acute or chronic PJI of TAA.

Diagnostic criteria of acute or chronic PJI (non-specific to TAA) is guided by the definition developed by the Musculoskeletal Infection Society, which was later modified in 2013 by the International Consensus Group on Periprosthetic Joint Infection (Table 1) [2]. Diagnosis of PJI requires the presence of one major criterion or presence of at least three of five minor criteria. Acute infections were defined by presentation within 90 days of index surgery and chronic infections after 90 days. Acute and chronic infections each have a different set of threshold levels for the minor criteria (Table 1) [2].

The current literature regarding ankle replacement is significantly limited in data available on PJI. Of the studies that reference diagnosis of PJI in TAA, only one study by Alrashidi et al. offers any explicit reference to a diagnostic algorithm used to classify patients with periprosthetic ankle infections [1]. While not explicitly delineated, the authors appear to invoke laboratory threshold measurements described by the International Consensus Group on Periprosthetic Joint Infection in their proposed diagnostic diagram. Our systematic review failed to identify any clinical study or publication that had implemented or referenced the diagnostic algorithm submitted by Alrashidi et al.

While Alrashidi et al. have presented the most comprehensive and systematic pathway to date specific to diagnosing a PJI in TAA [1], the criterion utilized in this pathway are derived from previously described literature specific to knee and hip arthroplasty [2,3]. TAA data is significantly more limited and thus difficult to establish statistically significant infectious indicators specific to the ankle joint. Alrashidi et al. present clinically useful data in their diagnostic algorithm including the presence of a sinus tract, cell count, and differential from synovial aspiration, culture from synovial aspiration, nuclear imaging studies and histological frozen sections. However, no sensitivities or specificities of the results have been described in determining PJI specific to TAA. Ferrao et al. also described similar work-up in diagnosing PJI in TAA including clinical history, physical examination, radiographic evaluation and laboratory values [4]. Pertinent history, such as sudden onset of pain, swelling, drainage, fever and associated clinical findings, such as tenderness, increased local temperature and effusion, were components concerning for PJI as described by the authors. This study presented a similar diagnostic pathway, including inflammatory markers and joint aspiration, and also made reference to the hip and knee arthroplasty literature in setting criteria and thresholds [5–7]. The trend of referencing hip and knee arthroplasty data in the work-up of PJI in TAA in our systematic review was common in the literature [8–14].

Patton et al. define PJI by positive preoperative or intraoperative cultures or the presence of chronic draining sinus tract, but do not provide reference for this definition [15]. Meyerson et al. similarly defined PJI by draining sinus tract, positive preoperative aspiration (purulent aspirate, positive Gram stain and/or elevated leukocyte count > 1,000 per mm^3) or positive intraoperative culture [16]. The authors subdivided infections into acute and chronic, but did not specify criteria for differentiating between the two. Kessler et al. defined PJI as clinical signs of infection plus at least one of the following: (1) same bacteria grown on two separate preoperative or intraoperative cultures, (2) visible pus surrounding the joint, (3) acute inflammation on histopathological examination (> 10 neutrophils/HPF) or the ability to probe the base of the wound to the implant) [10,11].

Other mentions of PJI in TAA in our literature search did not specifically describe the criteria used to reach that diagnosis [9,17–19]. Case reports of PJI in TAA were also described without defining parameters for diagnosis of acute or chronic infection [20,21]. Further review did demonstrate several manuscripts, which identified risk factors for PJI, including proximity to dental procedures or medical comorbidities but failed to provide a definition for diagnosis of acute or chronic PJI [22,23]. Our systematic review yielded definitions of acute and chronic PJI defined in total hip and knee literature, case

TABLE 1. Diagnostic criteria of periprosthetic joint infection according to the International Consensus Group on Periprosthetic Joint Infection

Major Criteria		
• Identification of 2 positive periprosthetic cultures with phenotypically identical microorganisms OR • Presence of a sinus tract communicating with the joint		
Minor Criteria		
• Elevated serum CRP AND elevated ESR • Elevated synovial fluid WBC count OR ++ change on leukocyte esterase test strip • Elevated synovial fluid PMN% • Positive histologic analysis of periprosthetic tissue • A single positive culture		
Threshold Levels for minor criteria for PJI		
Criterion	**Acute PJI**	**Chronic PJI**
ESR (mm/h)	Not helpful with no defined threshold	30
CRP (mg/L)	100	10
Synovial WBC count (cells/ µl)	10,000	3000
Synovial PMN %	90	80
Leukocyte esterase	+ OR ++	+ OR ++
Histologic analysis of tissue	> 5 neutrophils per HPF (x 400) in 5 HPF	

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; PMN%, polymorphonuclear neutrophil percentage; WBC, white blood cell count; HPF, high-powered field; PJI, periprosthetic joint infection, mm/h, millimeters per hour; µl, microliters. (Adapted with permission [2].)

reports, as well as suspected risk factors, signs, symptoms and history related to PJI.

In summary, there remains no definitive criterion in the literature for defining acute or chronic PJI after ankle arthroplasty. In the absence of specific diagnostic criteria for PJI of TAA, we may need to rely on the literature related to total hip arthroplasty and total knee arthroplasty to investigate this area further. A recent study published offers an evidence-based and validated definition for PJI of the hip and knee [24]. The criteria based on pretest probability offer each diagnostic criteria a score that is commensurate with the performance of the test in the pre-test probability and diagnostic odds ratio [24].

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QUESTION 2: What is the diagnostic "algorithm" for infected total ankle arthroplasty (TAA)?

RECOMMENDATION: Patients who present with clinical symptoms and signs of periprosthetic ankle infection (pain, erythema, warmth, sinus tract, abscess around the wound) and sinus tracts communicating with the ankle/subtalar joint are likely to have TAA infection.

In the absence of a sinus tract, elevated inflammatory markers (erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)) should prompt ankle joint aspiration for cell count, differential and culture. The joint aspiration is to be repeated.

If the same organism is identified in at least two cultures of synovial fluid, the patient is diagnosed to have an infection. If the repeat aspiration is negative, further investigation is warranted.

In patients not requiring surgical intervention for other reasons, nuclear imaging should be considered for diagnosis. If an operation is indicated, histologic examination (> 5 neutrophils/high-power field) or synovial fluid analysis is conducted to confirm infection.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Diagnosis of infected TAA is mainly guided by the periprosthetic joint infection (PJI) diagnostic criteria developed from the MusculoSkeletal Infection Society (MSIS) and the International Consensus Meeting [1–3]. Although the current PJI diagnostic criteria were developed based on hip and knee patients, the majority of the infected TAA clinical studies have employed the same or a variation of the MSIS criteria [3–9]. The major diagnostic criteria include (1) presence of a sinus tract which communicates with the joint or (2) two positive cultures isolating the same pathogen from the periprosthetic tissue or synovial fluid samples [1–3]. Minor criteria include elevation of inflammatory markers (CRP, ESR), elevated synovial fluid white blood cell (WBC) count or change on leukocyte esterase test strip, elevated synovial fluid polymorphonuclear cells, positive histologic analysis of periprosthetic tissue and single positive culture [1–3]. The above diagnostic algorithm was also recommended by the same authors [1–3].

Systematic literature reviews and meta-analyses have shown a 0 to 4.6% occurrence of deep infection after TAA [10,11]. Myerson et al. reported a 3.1% infection rate after TAA [6]. Their criteria for diagnosis was based on clinical findings of swelling, inflammation, drainage or persistent wound problem which prompted the protocol of joint aspiration for culture and microscopy. Synovial fluid analysis and lab analysis of inflammatory markers (CRP, ESR, WBC count) were tested to confirm infection. Patton et al. utilized similar criteria and reported a 3.2% rate of ankle PJI [7]. Usuelli et al. employed the same diagnostic criteria suggested by the MSIS and reported a 3.7% deep infection rate in the anterior approach group compared to a 1.4% deep infection rate in lateral approach group [9].

However, some authors have raised the possibility that the current MSIS guideline for diagnosis and treatment of hip and knee PJI may be different from the ankle joint, given the relatively thinner soft tissue envelope and limited number of patients who underwent successful joint-preserving revision ankle arthroplasty [3,5]. Moreover, no clinical study has validated utilization of the current hip and knee PJI diagnostic criteria for ankle PJI. Therefore, a high-quality clinical investigation is needed to validate the current criteria and algorithm for diagnosis and treatment of the ankle PJI.

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QUESTION 3: What tests are useful to investigate a possible infection of total ankle arthroplasty (TAA)? What are their thresholds?

RECOMMENDATION: Overall, the approach to a potentially infected TAA does not change compared to other periprosthetic joint infections (PJIs). There are no novel or unique diagnostic procedures for TAA infection, specifically. Joint aspiration or intraoperative tissue/synovial biopsies with microbiological cultures are the most important diagnostic tests for suspected TAA infections. In the absence of specific data related to TAA, the threshold for these tests should be derived from the hip and knee PJI literature.

LEVEL OF EVIDENCE: Strong

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

RATIONALE

The literature lacks information regarding a specific diagnostic work-up for infected TAA compared to PJI of other joints. Clinically, persistent pain with or without loosening of the components is believed to be a potential presentation for PJI of TAA [1–3]. According to some authors, the pain localization can hint at one diagnosis versus another; anteromedial pain is commonly caused by gutter impingement or medial ankle stress reaction, whereas more diffuse pain is usually associated with stiffness, loosening or infection [3]. A prior history of delayed surgical wound healing is often reported in patients with infection [4]. The presence of a sinus tract is definitive evidence of infection but is infrequently seen [4].

Ankle swelling and pain progressing to incisional discharge then dehiscence and rapid loosening are strongly suggestive of infection. In these cases, a joint aspiration or intraoperative tissue/synovial biopsies and microbiological work-up, remains the preferred method for diagnosis of TAA infections [2–7]. The microbiological techniques (culture, polymerase chain reaction) are not specific for TAA infections. In infected TAA literature that identifies the causative pathogen, there is a trend towards TAA PJI being affected by a higher proportion of gram-positive microorganisms compared to other PJIs and a smaller proportion of gram-negative bacteria [4,5]. Of note, the microbiological evaluation in one study found no single gram-negative bacteria among 19 cases of infected TAA [7]. Intra-articular leukocyte differentiation, leukocyte esterase, intra-articular C-reactive protein, or alpha-defensin immunoassays of prosthetic joint samples have not yet been sufficiently validated for TAA PJI [8]. Other than during the initial work-up to rule out infection, systemic serum inflammatory markers are practically of no additional advantage. Many authors do not dogmatically recommend their use [3]. Likewise, imaging techniques do not prove infection but may show the localization of abscesses or may confirm implant loosening [1]. Hsu et al. suggested that more than 10 leukocytes per high-power microscopic field in the synovial biopsies would be suggestive of infection [1]. Other groups have reported that >5 leukocytes per high power field in frozen section microscopy may be indicative of PJI [5,7]. However, these approaches are not shared with the majority of author groups and convincing data in favor of microscopic leukocyte counting for TAA specifically are lacking.

Ultimately, there is little consensus regarding the work-up for TAA PJI. Many diagnostic tools are used based on provider preference, with only aspiration and fluid analyses being universally endorsed in the literature.

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QUESTION 4: What are the indications for aspiration of a possibly infected total ankle arthroplasty (TAA)?

RECOMMENDATION: Whenever a periprosthetic joint infection (PJI) of a TAA is clinically possible or suspected, especially when elevated erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) levels exist, and in correspondence to the literature on PJI in total hip and knee arthroplasties, joint aspiration is indicated.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

We performed a systematic review of the literature regarding the research question found above as recommended: A PubMed Search for the MeSH Terms ("arthrocentesis"[MeSH Terms] OR "arthrocentesis"[All Fields] OR ("joint"[All Fields] AND "aspiration"[All Fields]) OR "joint aspiration"[All Fields]) AND ("arthroplasty, replacement, ankle"[MeSH Terms] OR ("arthroplasty"[All Fields] AND "replacement"[All Fields] AND "ankle"[All Fields]) OR "ankle replacement arthroplasty"[All Fields] OR ("total"[All Fields] AND "ankle"[All Fields] AND "arthroplasty"[All Fields]) OR "total ankle arthroplasty"[All Fields]) was performed on February 16, 2018. A total of n = 10 results were found.

Additionally a PubMed Search for the MeSH Terms ("infection"[MeSH Terms] OR "infection"[All Fields]) AND ("arthroplasty, replacement, ankle"[MeSH Terms] OR ("arthroplasty"[All Fields] AND "replacement"[All Fields] AND "ankle"[All Fields]) OR "ankle replacement arthroplasty"[All Fields] OR ("total"[All Fields] AND "ankle"[All Fields] AND "arthroplasty"[All Fields]) OR "total ankle arthroplasty"[All Fields]) was performed on February 17th, 2018. A total of n = 200 results were found. After exclusion of irrelevant manuscripts or duplicates, only four publications remained that can be considered a "match" regarding a specific answer to the research question.

Investigation of a prosthetic joint for possible infection, including the ankle, commences with detailed history-taking, physical examination and ordering a series of laboratory tests. There is no gold standard for diagnosis of PJI and because of this, we must rely on a combination of diagnostic techniques to reach or refute the diagnosis of PJI. The serum laboratory tests that should be ordered include ESR, CRP and potentially other tests, such as D-dimer levels. If these laboratory tests are elevated or with normal serological tests and high clinical suspicion for infection, the next line of investigation is believed to be joint aspiration.

The synovial fluid obtained, if any, should be sent for analyses that include total white blood cell count, neutrophil count and the percentage of neutrophils, as well as analyses for biomarkers, such as leukocyte esterase and alpha-defensin. The joint aspirate is also cultured to identify the potential infecting pathogen.

Although the algorithm for investigation of PJI in hip and knee arthroplasty has been well studied and the optimal threshold for parameters, such as cell count and neutrophil differential, determined, there is little data related to PJI of TAA. In the absence of such data, we believe that TAA should also be investigated in a similar fashion to hip and knee arthroplasty. In fact, our search determined that most studies related to TAA use the MusculoSkeletal Infection Society criteria and extrapolate data published in total hip and knee arthroplasty literature to TAA [1]. In one study, Alrashidi et al. recommended that aspiration for synovial fluid analysis should be considered if the ESR and CRP are elevated [2]. This has been corroborated by other studies in recent years, confirming the utility of aspiration to help gauge the presence of inflammation or infection around a TAA [3–5].

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QUESTION 5: What is the best technique for performing aspiration of patients with total ankle arthroplasty (TAA)?

RECOMMENDATION: In the absence of evidence, we recommend that ankle joint aspiration to evaluate for periprosthetic joint infection (PJI) be performed under sterile conditions via the anteromedial approach. Ultrasound guidance may be used if available but is not necessary to obtain an acceptable synovial fluid sample.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

In the setting of suspected ankle PJI based on preoperative history, physical, laboratory values and imaging modalities, preoperative aspiration can be useful and may reveal an organism in 50 to 60% of cases [1]. Landmark-based aspiration using a sterile technique via an anteromedial approach performed in the office is most commonly performed in order to obtain ankle synovial fluid for analysis. Imaging guidance via computed tomography or ultrasound is not usually necessary since the ankle joint is relatively simple to aspirate [2]. Ultrasound guidance may provide higher accuracy if available based on cadaver studies evaluating injections, which suggested 85% accuracy without ultrasound and 100% accuracy with ultrasound [3,4]. However, another study demonstrated 100% accuracy in ankle joint needle insertion in a cadaver study using palpation technique only [5]. In the setting of infection, there is typically excess fluid resulting in simpler access to the ankle joint for aspiration. Thus, aspiration can be performed without necessarily using ultrasound guidance.

The ankle can be accessed via several approaches. The most common approach is the anteromedial approach, which is just medial to the tibialis anterior tendon at the level of the ankle joint.

No difference was seen between anteromedial or anterolateral approaches in a cadaver study when performed by orthopaedic trainees, and there was an 80% success rate of being intra-articular with both approaches [6].

The risk of bacterial contamination of the joint after aspiration has not been studied. There is some literature discussing septic arthritis after corticosteroid injection. One report indicated an incidence of 0.5% in a population of patients with rheumatoid arthritis on immunosuppressant medication [7]. In the general population, infection after cortisone injection is reported to range between 1 in 3,000 to 1 in 16,000 [8,9]. It is generally thought to be very rare when a basic sterile technique is used.

We recommend that the site of ankle aspiration is wiped with alcohol and then prepared with the use of another antiseptic agent, such as povidone-iodine or chlorhexidine. Although not absolutely necessary, the site of aspiration may be isolated with the use of sterile towels. The aspiration may be performed in the office setting or the operating room suite, depending on the infrastructure in each facility.

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QUESTION 6: Should aspiration of the ankle with an antibiotic spacer be performed prior to reimplantation?

RECOMMENDATION: We recommend that aspiration of the ankle with an antibiotic spacer prior to a second-stage reimplantation should be strongly considered. Available studies indicate that a positive culture of the aspirate in this setting is predictive of residual infection, while a negative aspirate culture does not rule out infection and should be interpreted in light of other clinical indicators and laboratory values.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 92%, Disagree: 8%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

There have been no studies in the total ankle arthroplasty (TAA) literature that have evaluated the utility of aspiration of an antibiotic spacer as part of a two-stage revision for infected total ankle arthroplasty. In a review article, Alrashidi et al. stated that reimplantation should only be undertaken once the infection is eradicated as indicated by clinical history and examination, serological testing and synovial fluid aspiration [1]. However, no references or evidence is cited to support this assertion. Two large series on the treatment of infected TAA each included two-stage revision with use of an antibiotic spacer as a treatment strategy [2,3]. However, neither study included preoperative aspiration of the antibiotic spacer in the methodology. Of note, Myerson et al. did routinely perform intraoperative examination of tissue and fluid by microscopy during definitive reconstruction surgery in order to evaluate for the presence of polymorphonuclear (PMN) leukocyte count > 5 per high power field or the presence of organisms on Gram stain [2]. If either criterion was met, repeat debridement with antibiotic cement spacer exchange was performed and the definitive reconstruction was deferred.

There have been numerous studies in the total hip and knee replacement literature investigating the utility of aspiration of antibiotic spacers. While these have provided valuable data, it should be noted that these studies were largely retrospective and non-uniform. The definition of the presence of infection was also not clear in some of these studies, and positive culture was considered by many studies as the gold standard. Some studies also correlated the results of the aspiration and intraoperative findings with the ultimate success or failure following reimplantation. The studies also have significant variability in the duration of antibiotic treatment as well as variability in the presence/absence and duration of an antibiotic holiday.

Studies regarding aspirate cultures of antibiotic spacers for infected total knee arthroplasty reported generally better specificity than sensitivity. Specificity ranged from 61 to 100% while sensitivity ranged from 0 to 83% [4–8]. Positive predictive value ranged from 0 to 100% while negative predictive value ranged from 74 to 97% [4–8]. Aside from cultures, additional aspiration tests have been evaluated for accuracy. There is significant variability across reported cut-off values and sensitivity and specificity rates for white blood cell count and PMN% of preoperative aspirates [9–12].

One argument for routine aspiration of an antibiotic spacer of the hip or knee prior to reimplantation revolves around the relatively low cost, simplicity and low risk of the procedure. However, in the setting of a temporary antibiotic spacer of the ankle, there is no evidence regarding the success rate of attempted aspirations.

One challenge that exists is the interpretation of a dry aspiration. In the hip, consideration has been given to performing a saline

lavage in order to improve the yield of aspiration. Newman et al. reported that saline lavage predictably affected the results of synovial cell counts and their diagnostic utility but has a less substantial effect on culture results [11].

In the absence of concrete evidence, with reliance on the available data from the hip and knee literature and taking into account the simplicity of aspirating an ankle joint, we recommend that aspiration of the ankle with an antibiotic spacer be strongly considered prior to reimplantation. The analysis of the aspirate fluid, if obtained, will provide valuable data that can influence the intended procedure and the ultimate success and failure of reconstruction.

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QUESTION 7: Is there a role for measuring synovial biomarkers for diagnosis of infected total ankle arthroplasty (TAA)?

RECOMMENDATION: Based on the hip and knee arthroplasty literature, measuring synovial biomarkers may play a role in the diagnosis of infected TAA. The diagnosis of periprosthetic joint infection (PJI) in the setting of a TAA can be confirmed with cultures, provided that a plausible pathogen is recovered in the context of a compatible clinical picture. In the absence of a positive culture, synovial biomarker analysis may help in establishing the diagnosis.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 92%, Disagree: 8%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

TAA has emerged as a successful procedure, improving both pain and function in patients with end-stage arthritis of the ankle, with reported rates of infection ranging from 0 to 4.6% [1]. A specific approach does not yet exist for the diagnosis of PJI in TAA. However, the traditional approach for the diagnosis of PJI in other joints involves joint aspiration and sampling of the synovial fluid for analysis involving synovial white blood cell (WBC) count and differential fluid culture, as well as serum WBC count, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels [2,3].

Elevation of several synovial biomarkers has been identified as indicators of potential PJI, including WBC count, percentage of polymorphonuclear cells (PMN%), α-defensin, leukocyte esterase (LE), interleukin IL-1a, IL-1, IL-6, IL-8, IL-10, IL-17, granulocyte colony-stimulating factor (G-CSF), vascular endothelial growth factor (VEGF), CRP, neutrophil elastase 2 (ELA-2), lactoferrin, neutrophil gelatinase-associated lipocalin (NGAL), resistin, thrombospondin and bactericidal/permeability-increasing protein (BPI) [4–6].

Among the previously-mentioned synovial biomarkers, α-defensin is regarded as the most accurate single test for the diagnosis of PJI, with a sensitivity of 97% and a specificity of 96% [5]. Therefore, the accuracy of α-defensin is closest to the 2013 International Consensus Meeting (ICM) criteria for the diagnosis of PJI [6]. Alpha-defensin also appears to provide the most consistent results, regardless of the causative microorganism or its virulence. Its accuracy even remains unaffected in the setting of antibiotic administration to the patient prior to obtaining the synovial fluid sample [4,5,7]. IL-8 has been shown to follow α-defensin in terms of performance, while the accuracy of synovial fluid culture has been shown to have a sensitivity of 62% and specificity of 94% [5]. Synovial fluid leukocyte count (sensitivity of 89% and specificity of 86%) and PMN percentage (sensitivity of 89% and specificity of 86%) both demonstrate accuracy in diagnosing PJI [5,6]. However, they are already part of the six minor criteria for the diagnosis of PJI according to the ICM 2013 definition of PJI [6]. There is great controversy regarding the cutoff point used for the synovial leukocyte count and PMN percentage, which prevents their use as stand-alone diagnostic tests [4,5,8–12].

LE, with a sensitivity of 77% and specificity of 95%, has the advantage of being inexpensive [5,13–16]. However, there is a level of subjectivity present with the interpretation of LE results, in addition to the possibility of the presence of blood in the fluid affecting the results.

The combination of two or more markers to detect PJI has been studied. It has been shown that the combination of synovial fluid α-defensin and CRP provided a sensitivity of 97% and a specificity of 100% in diagnosing PJI [17]. The combined use of synovial CRP and adenosine deaminase (ADA) improves the positive predictive value [18]. A synovial fluid CRP should be included in the synovial fluid analysis and correlated with other lab markers [17].

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QUESTION 8: What is the role of molecular techniques for detection of pathogen deoxyribonucleic acid (DNA) (polymerase chain reaction (PCR) or next-generation sequencing) in patients with infected total ankle arthroplasty (TAA)?

RECOMMENDATION: Molecular techniques, particularly next-generation sequencing and the Ibis T5000 technology, have the potential to be used as an important adjunct in the diagnosis of bacterial infection following TAA, although sufficient clinical evidence is lacking.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

The culture of multiple periprosthetic tissue samples is currently considered the gold standard for microbiological diagnosis of periprosthetic joint infections (PJIs) [1]. However, biofilm-associated infections are not easily detected by culture-based methods and are often resistant to conventional antimicrobial therapy. Therefore, it seems imperative to promptly investigate and subsequently integrate molecular diagnostic techniques into the clinical practice for the management of PJI [2].

The most common molecular techniques that have been used to diagnose PJI are both based on PCR: specific PCR and broad-range PCR [3]. Specific PCR targets a single bacterial species (e.g., *Staphylococcus aureus*) or a group of closely-related species (e.g., all staphylococcal species). These are typically considered real-time PCR assays. Specific PCRs can be used in the diagnosis of any targeted pathogen with extreme sensitivity, potentially detecting even a single copy of the target DNA. This approach provides accurate results within hours and has the advantage of singling out any organisms deemed as significant, thereby making contamination easier to control for, as well as making quantification possible [3].

Broad-range PCR, in contrast to specific PCR assays, provides the opportunity to detect DNA from any pathogen rather than a specific preset of expected pathogens. Almost all broad-range PCR techniques utilized in diagnostic microbiology laboratories are based on the gene coding for the small subunit of the bacterial ribosome (16S rDNA). The main limitations of broad-range PCR relate to inherent problems with contamination and sensitivity. Contamination arises from bacterial DNA present in PCR reagents or inadvertently introduced during the collection and handling of the sample, particularly if additional fluids are added to the culture sample during transport or laboratory processing [4]. Unfortunately, these "contaminant" bacteria detected with broad-range PCR are closely related to the microorganisms that cause low-grade

PJI, making the distinction between true-positive versus false-positive PCR results challenging. For these reasons, broad-range PCR has not yet been integrated into the standard routine diagnostic procedure of PJI by most laboratories, but this technique is a valid option to be applied to the diagnosis of synovial fluid or periprosthetic tissue infections [5,6].

Comparing the specific and broad techniques, one study found the sensitivities of specific PCR for detection of *Propionibacterium acnes* and *staphylococcus spp*. in sonication fluid from prosthetic shoulder infections to be 89% and 97%, respectively [7]. In contrast, broad-range PCR of tissue cultures in patients with PJI has previously demonstrated a sensitivity of only 50% [8].

The arrival of high-throughput (next-generation) sequencing techniques has enabled the generation of thousands of individual sequences from a single broad-range PCR [3]. This approach seems to be promising in aiding in surgical site infection and PJI detection, since it provides detailed information on the bacterial population present in prosthetic joint samples [3]. The next-generation technique of pyrosequencing allows for massively parallel, rapid identification of pathogens at a much lower cost per base than the traditional sequencing. The greater breadth and depth of pyrosequencing, in which hundreds of thousands of sequences can be generated in a single run, means that low abundance species have a higher chance of being detected [3].

When comparing molecular and microbiological techniques on PJIs, culture and PCR have shown similar sensitivities (72.6% and 70.4%) and specificities (98.3% and 97.8%) [9,10]. While using a combination of 16S rDNA PCR and lateral flow immunoassay, the 16S recombinant DNA (rDNA) test system provided a diagnostic result within 25 minutes in 97% of all patients. This can be juxtaposed to the microbiological culture of synovial fluid, which achieved a lower sensitivity than that of the 16S rDNA test with 80% [11]. In terms of cost, molecular diagnosis may be a more expensive diagnostic method than bacterial culture with a cost-effectiveness that has not yet been evaluated [12]. The direct detection of bacterial 16S rDNA shows encouraging results and warrants further evaluation in larger patient cohorts [11].

While molecular techniques have shown to be important in diagnosing PJI in orthopaedic fields other than foot and ankle, they have not been well-studied in the setting of an infected TAA. In one of the few studies identified studying the utilization of molecular techniques in the foot and ankle, Stoodley et al. evaluated several techniques to ascertain the presence of a bacterial infection in an explanted TAA that had an initial negative culture. The techniques included the Ibis T5000, real time-polymerase chain reaction (RT-PCR), a direct culture of the ankle hardware, confocal microscopy, and fluorescent in situ hybridization (FISH) [13].

The Ibis T5000, a research use only (RUO) technology based on the combination of PCR amplification of highly conserved pathogen genomes with high-performance electrospray ionization mass spectrometry and base-composition analysis, is able to tease out a variety of organisms (including bacterial and viral) down to the species level [14]. Data points include number of genome copies, relative organism abundance and antibiotic sensitivity [15,16]. Based on Ibis testing, Stoodley et al. were able to identify the presence of *S. aureus*, *S. epidermidis* and the methicillin-resistant *mecA* gene in tissue on the removed TAA hardware [13]. Additionally, the Ibis detected that there was close to ten times more *S. aureus* in comparison to the *S. epidermidis*. Of all the techniques investigated, the authors proposed the Ibis T5000 technology to have the most potential in aiding with clinical detection of PJI with TAA [13].

In addition to the Ibis system, the authors used RT-PCR in order to detect metabolically active *S. aureus* [13]. The authors were able to harvest ribonucleic acid (RNA) from a tissue sample and after converting the RNA to complementary DNA via reverse transcription, they utilized specific PCR primers for the bacterial glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and histidine ammonia-lyase (*hutH*) genes [17–19]. The study demonstrated the presence of *S. aureus* messenger RNA for both the GAPDH and the *hutH* genes [13].

Another technique was a direct culture of the tibial metal component of the removed ankle hardware. After a detailed agar preparation protocol, the tibial component was placed in a beaker in which an agar formed. After incubation, the number of bacterial colony-forming units (CFUs) on the agar was eventually estimated. The authors reported approximately 1000 CFUs spread across the entire tibial component and composed of methicillin-resistant *Staphylococcus aureus* (MRSA) and methicillin-resistant *S. epidermis* [13].

Confocal microscopy was also implemented for viability determination after staining and using a 488nm excitation wavelength to identify bacteria as living or dead. Fluorescent in situ hybridization (FISH) was also utilized using fluorophore-labeled 16S rDNA sequences specific for *S. aureus* [20–22]. A red Syto59 fluorescent nucleic acid stain was used to stain all bacterial and host nuclei, allowing *S. aureus* to be the only species stained both red and green. Bacteria that were stained with Syto59 solely were distinguished from host nuclei on the basis of size [22,23]. Confocal microscopy and FISH demonstrated a scattered distribution of biofilm formation, with clusters of bacterial colonies on tissue, the talar component edges, the polyethylene bearing surface and the tibial component. FISH testing also indicated that bacterial growth was predominantly *S. aureus* and *S. epidermidis* to a lesser extent [13].

These findings presented by Stoodley et al. offer to be an important diagnostic step to gauge the presence of a bacterial infected TAA [13]. However, further research is necessary to decide the true clinical utility of these techniques.

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QUESTION 9: Should culture samples be taken during all revision total ankle arthroplasty (TAA)?

RECOMMENDATION: We recommend that intraoperative cultures be taken during revision TAA. The result of intraoperative cultures should be interpreted together with clinical suspicion for infection and the results of the laboratory and imaging investigations. We also recommend that multiple tissue specimens be collected. Given a lack of evidence for routine intraoperative cultures for revision TAA literature, this recommendation is based on analogous evidence in the total hip and knee replacement literature.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

There have been no studies in the TAA literature that have evaluated the utility of routine intraoperative cultures for all revision TAA cases. Multiple case series and review articles on revision TAA have been published which do not specifically advocate for or against this practice [1–4]. Jonck et al. do, however, recommend curettage of any encountered cysts at the time of revision and advise that cyst material should be sent for cell count, microbial culture and histopathology [3]. However, no data is included regarding previous results and utility of these samples.

There have been multiple studies in the total hip and knee replacement literature investigating the role of routine cultures taken during revision arthroplasty for presumed aseptic failure. Barrack et al. published on a series of revision total knee replacements with unexpected positive intraoperative cultures [5]. There were 41 cases with positive cultures out of 692 total cases. Twenty-nine of these cases had only one positive culture without additional evidence of infection and were considered false positives. None of the presumed false positives had long-term signs of infection or required additional surgery. The other 12 cases had multiple positive cultures or one positive culture and an abnormal preoperative inflammatory marker or synovial aspirate. These cases were treated with a four to six week course of antibiotics and two of these patients presented with early recurrent infection requiring a two-stage exchange. An additional patient had aseptic loosening requiring revision at six years, at which time there was no sign of infection and negative intraoperative cultures. The authors recommended routinely sending at least five sets of cultures in the setting of abnormal preoperative inflammatory markers, abnormal synovial aspirate or tissue appearing concerning for infection intraoperatively at the time of revision.

Jacobs et al. reported on 679 cases of revision hip or knee arthroplasty for presumed aseptic failure [6]. Infection was defined by the presence of two or more positive intraoperative cultures with the same organism. The incidence of unsuspected infection was 10%. For total knee replacements, patients diagnosed with infection went on to require repeat revision for recurrent infection at a higher rate compared with patients who were not diagnosed with infection at initial revision. For total hip replacements, there was no significant increased rate of recurrent infection requiring revision. The authors emphasized the importance of improved preoperative work-up prior to revision total joint arthroplasty to minimize the number of unsuspected prosthetic joint infections.

Given that there is a small but significant incidence of unsuspected joint infection in hip and knee arthroplasty, there is likely a similar incidence of unsuspected TAA infection amongst presumed aseptic failures. Routine cultures at the time of revision for aseptic failure may help to identify unsuspected infections. However, even the literature for hip and knee replacement does not provide significant evidence to suggest how to intervene once the diagnosis is made and whether long-term outcomes can be improved once intraoperative cultures lead to the diagnosis of periprosthetic joint infection (PJI).

Therefore, we recommend that all patients undergoing revision ankle arthroplasty be investigated for PJI, which includes measuring serum markers, aspiration of the joint, intraoperative evaluation (which may include histology) and any other necessary tests. The

result of intraoperative culture during revision ankle arthroplasty can then be interpreted in light of laboratory and imaging investigations and any clinical suspicion for infection.

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2.2. DIAGNOSIS: NON-TOTAL ANKLE ARTHROPLASTY-SPECIFIC

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QUESTION 1: What is the optimal number of samples for culture in patients undergoing surgery for foot and ankle infections?

RECOMMENDATION: The optimal number of samples for culture in patients undergoing surgery for foot and ankle infections is unknown. We recommend that multiple tissue samples be taken.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

Our search of the literature did not reveal any data regarding the optimal number of culture samples that should be taken during foot and ankle surgery. However, there is high-level evidence in the periprosthetic joint infection (PJI) literature regarding this topic. Bémer et al. conducted a prospective multicenter study evaluating the minimum number of samples required to make an accurate diagnosis of PJI [1]. They determined that four samples were sufficient for diagnosing PJI with the highest mean percentage of agreement (98.1% and 99.7%, respectively) in regards to the bacteriological criterion and diagnosis of confirmed PJI.

Atkins et al. performed a prospective study assessing the effect of sample number on the ability to diagnosis PJI [2]. Their study recommended sending five to six specimens and defined a cutoff of three or more positive operative cultures yielding an indistinguishable organism for definite diagnosis. This recommendation achieves an extremely high specificity, but an impractical sensitivity (it would require too many samples). In order to achieve both excellent sensitivity and specificity, five to six specimens with two or more culture-positive samples are recommended to diagnose infection.

The Infectious Diseases Society of America guidelines [3] provide moderate evidence from more than one well-designed clinical trial, without randomization (B-II evidence) recommending at least three (and optimally five or six) intraoperative tissue samples be submitted for aerobic and anaerobic culture to diagnose a PJI.

The majority of studies related to this subject in regards to the foot and ankle relate to the management of patients with diabetic foot ulcer and osteomyelitis. The available studies have revealed that the yield of culture is dependent on how these culture samples are taken (e.g., swab, bone biopsy and so on) and did not evaluate the influence of the number of culture samples taken.

In 144 diabetic foot ulcer patients with suspected osteomyelitis, ulcer swab and bone biopsy specimens were taken. The authors found that there is poor reliability of the ulcer swab culture in identifying the pathogens causing osteomyelitis in this patient population. When used in conjunction with bone biopsy specimen culture, there may be a more reliable isolate for effective management [4]. Another study reported that swab cultures may have utility for guiding the antibiotic selection for management of low-grade infection. In the setting of higher grade infections, deeper tissue culture and biopsy are necessary [5].

Although there is limited literature guiding the number of samples necessary to obtain for foot and ankle infections, this indicates the need for research in this area. Given the extent of studies conducted in other areas of orthopaedic surgery, similar studies should be conducted in the foot and ankle area to better guide appropriate management.

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QUESTION 2: What strategies can be implemented to help isolate the causative organism in patients with infection of the foot and ankle?

RECOMMENDATION: Transfer of synovial aspirate in blood culture bottles, obtaining deep biopsy of tissues and bone, obtaining multiple samples, increasing incubation period of cultures and the use of molecular techniques for culture negative cases are some of the strategies that can help improve the ability to isolate the causative organism(s) in infections of foot and ankle.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Given the risk of false positive cultures, it is important to holistically evaluate patients who are suspected to have an infection of the foot and ankle following an algorithm suggested by the Musculoskeletal Infection Society's definition of periprosthetic joint infection (PJI) [1]. It should be noted that these diagnostic criteria have not been evaluated for infections of the foot and ankle. Isolation of the causative organism in orthopaedic infections can be challenging. Culture-negative infections in hip and knee arthroplasty are not uncommon. Using the experience gained from hip and knee arthroplasty surgery and relying on the literature from the same field of orthopaedics, the following strategies may be implemented to improve the yield of culture in foot and ankle infections.

Synovial Aspirate

Synovial aspiration provides a variety of opportunities for testing, including synovial leukocyte esterase (LE) testing, synovial fluid white blood cell (WBC) count and polymorphonuclear (PMN) percentage, alpha-defensin levels, and Gram stain and cultures. In the hip and knee literature, application of synovial fluid to a simple urine test strip evaluating leukocyte esterase levels can be an accurate marker of PJI (sensitivity of 81-93%, and specificity of 87-100%) [2–4]. False positives do occur, and a positive LE strip should not be used in isolation to diagnose PJI. Although specific levels of synovial fluid WBC count and PMN percentage have been reported for diagnosis of PJI in the hip and knee, there is no literature specific to the foot and ankle [5–10]. Although alpha-defensin has been evaluated and is a promising new serologic test in the hip and knee, there is no literature to support its utility in evaluating infections of the foot and ankle [11,12]. While there is currently no literature defining criteria concerning LE, synovial fluid WBC and PMN percentage, or alpha-defensin levels for acute or chronic infection in the native or prosthetic ankle or soft tissue of the foot and ankle, we must use clinical suspicion and abnormal levels established by the adult hip and knee PJI literature until further studies evaluate abnormal levels in the foot and ankle. Several studies have demonstrated low sensitivity with Gram stain testing and poor utility for the diagnosis of PJI [13–15]. However, Gram stain and culture may provide additional information concerning likely causative organism and may help corroborate culture results with Gram stain findings in instances of potential contamination. There is no literature concerning the utility of Gram stain testing in the infected foot or hindfoot, and further studies may be necessary to better understand whether Gram stains aid in the diagnosis or treatment of suspected ankle or hindfoot native infection or PJI.

Blood Culture

Given the role of medical management in PJI with sepsis or bacteremia as well as prognosis, we recommend routine blood cultures for patients with systemic manifestations of infection. Although bacteremia is acknowledged as an etiology of PJI, the role of blood cultures in the diagnosis of PJI remains unknown. Currently, most guidelines state that blood cultures can be considered in light of systemic manifestations of infection but are not routinely obtained [16,17].

However, the care of patients diagnosed with PJI involves a multidisciplinary team, including infectious disease, internal medicine, emergency medicine and critical care physicians. Blood cultures are a staple in the work-up of many other medical conditions and may be acquired by the treating surgeon or more often a collaborating physician. Klement et al. investigated the role that blood cultures play in PJI patients and what association a positive result has on treatment outcome [18]. Blood cultures were obtained from 53.1% of patients (170/320) presenting with PJI at the time of diagnosis, with the same organism being identified 86.0% of the time in both blood and operative cultures. Furthermore, patients with positive blood cultures demonstrated a decreased treatment success rate compared with those with negative blood cultures. Therefore, the presence of positive blood cultures at the time of PJI diagnosis may not only impact the medical management of patients but also serve as a prognosticator towards the likelihood for success.

Tissue vs. Swab Culture

We strongly recommend against the routine use of swabs for surgical culture. In a study of 156 aseptic and septic hip and knee revision arthroplasties, Aggarwal et al. demonstrated that tissue cultures were positive in a higher percentage of septic cases than swab cultures: 28 of 30 (93%) versus 21 of 30 (70%). Surprisingly, tissue cultures were positive in two of 87 aseptic cases (2%), while swab cultures were positive in 10 of 87 (12%) [4]. Tissue cultures demonstrated higher sensitivity, specificity, positive predictive value, and negative predictive value for diagnosing PJI than swab cultures, while swab cultures had more false-negative and false-positive results than tissue cultures [4]. Because swab cultures pose a greater risk of failing to identify or incorrectly identifying causative organisms in PJI, we believe the use of swab cultures in obtaining intraoperative culture specimens should be discouraged.

Number of Intraoperative Samples

We recommend obtaining multiple intraoperative tissue samples for culture in suspected PJI cases or infections of the foot and ankle. Historic hip and knee protocols for periprosthetic tissue collection have been established with a target of five samples [19–21].

However, sensitivity and specificity are maximized with five to six periprosthetic samples being collected [13]. Given the relative difference in the surgical field area in hip and knee versus foot and ankle procedures, culture specificity and soft tissue preservation should not be compromised by taking more than six samples.

Holding Preoperative Antibiotics

We recommend routine holding of perioperative prophylactic antibiotics in all cases with a high suspicion for PJI in which a causative organism has not been isolated. There is mixed literature related to whether routinely holding antibiotics prior to surgery is necessary with no literature specific to foot and ankle. Recent antibiotic administration has been shown to decrease tissue culture sensitivity [22]. However, two prospective (one randomized) studies have demonstrated that prophylactic preoperative antibiotics do not impair the sensitivity of traditional intraoperative cultures [23,24]. Therefore, mandatory withholding of prophylactic antibiotics is not justified in cases where the pathogen has already been isolated preoperatively. Special consideration should be taken into account in cases in which PJI is diagnosed or suspected, but a pathogen has not been identified. In these cases, the use of prophylactic antibiotics is dependent upon clinical judgment.

Frozen Section

Intraoperative frozen section (FS) histopathology should be considered a valuable adjunct to the diagnostic work-up for patients undergoing revision arthroplasty in culture-negative PJI when the potential for infection remains following a thorough preoperative evaluation, but limitations should be noted. An intraoperative FS looking for acute inflammatory neutrophils in tissue obtained from the joint capsule or periprosthetic membrane has been used for intraoperative decision making. Although multiple studies have demonstrated that intraoperative FS of periprosthetic tissues performs well in culture-positive PJI with relatively high specificity, FSs lack the ability to isolate the organism and consistently demonstrated poor sensitivity and ability to rule out this diagnosis [25–29]. The optimum diagnostic threshold (number of PMNs per high-power field (HPF)) required to distinguish PJI from aseptic failure ranges from 5 to 23 with no clear threshold [30–32]. Although the appropriate thresholds for diagnosing PJI in histological analysis is controversial, a maximum tissue concentration between 5 to 10 PMN/HPF in each of 5 or more HPF seems to carry the best diagnostic performance. Neutrophils entrapped in superficial fibrin are not predictive of infection and submitting samples obtained by sharp dissection instead of cautery will help limit false positive diagnoses due to thermal artifacts.

Atypical Cultures – Acid Fast Bacilli (AFB) and Fungal

Mycobacterium and fungi are rare causes of PJI [33–35]. We recommend against routine AFB and fungal testing in suspected septic or aseptic failure except when warranted by patients who are at risk for such infections or when other traditional pathogens have not been identified where clinical suspicion remains elevated. Evidence has demonstrated that routine AFB and fungal testing in presumed aseptic cases does not yield clinically important results nor is it cost-effective [36]. However, when mycobacterium and fungal organisms are considered, AFB and fungal-selective media must be included, and it should be noted that prolonged culture may be required according to national laboratory standards. One should expand diagnostic testing to include tissue samples for histological examination, especially in patients with high clinical suspicions of infection. Resistance of Candida species to fluconazole has been reported in the literature, and susceptibility testing may be requested when resistance to fluconazole is suspected based on isolated species. Antifungal susceptibility testing remains less well developed and utilized than antibacterial testing.

Culture Incubation Period

We recommend that routine cultures be maintained for 5 to 14 days. If PJI by low virulence organisms is suspected, preoperative cultures failed to demonstrate bacterial growth, or if the clinical picture is consistent with culture-negative PJI, the cultures should be maintained for at least 14 days. Evidence demonstrates that extending periprosthetic cultures to two weeks significantly increases culture sensitivity while not increasing the risk of contaminants [21,37–39]. However, we recommend holding cultures for only five days in patients in whom the causative organism has been isolated preoperatively.

Routine Sonication of the Prosthesis or Implants

We are unable to recommend for or against the routine utilization of sonication of explants. The consideration of its use should be limited to cases with high suspicion for PJI or proven PJI cases in which preoperative aspiration fails to yield positive culture. Explant sonication utilizes ultrasonic energy to a fluid immersed sample to dislodge bacteria embedded in biofilm and has been shown to increase the likelihood of isolating pathogens without increasing the risk of contaminants [40–46]. Several studies have demonstrated better efficacy in dislodging bacteria from biofilm on titanium or stainless steel implants and improved sensitivity of cultured samples compared to scraping with a surgical blade [42]. In the hip and knee arthroplasty literature, Trampuz et al. demonstrated that sonication increases the rate of positive cultures and the sensitivity of sonicated fluid to identify that a causative organism was superior to that of tissue culture (78.5 vs. 60.8%) [40]. Similarly, Holinka et al. and Shen et al. found sonicate fluid to have a sensitivity greater than tissue (83.3 vs. 72.2%) as well as synovial fluid (88 vs. 64%), respectively [47,48]. When comparing sensitivities of cultures from sonicated fluid versus tissue samples, Yano et al. identified a sensitivity of 90.4 vs. 56.8%, respectively, in a large cohort of 180 fracture fixation explants [49]. In a mixed cohort of explanted joint prostheses and fracture fixation explants, Portillo et al. demonstrated improved sensitivity of cultures with 100 vs. 87 vs. 59% following inoculation of sonicated fluid in blood culture bottle compared to regular culture of sonicated fluid and tissue cultures, respectively [50]. The sonication of explants is an expensive procedure that is likely not justified in most assumed aseptic cases. In a large prospective study, the greatest benefit of explant sonication over standard tissue culture was found when antibiotics were provided within two weeks of surgery [41]. Although early literature is promising with possible greater sensitivity and improved bacteria detection with sonication, more literature is necessary to demonstrate the clinical efficacy and relevance prior to supporting broad utilization in the foot and ankle.

Fluorescence In-situ Hybridization (FISH)

We recommend against the routine use of FISH in order to evaluate for suspected infection of the foot and ankle. This process utilizes fluorescent probes to stain bacterial ribosomal ribonucleic acid, thus allowing direct visualization of the organisms in a native biofilm. Although FISH techniques have proven to be a highly reliable nonculture method to demonstrate the presence of pathogens even in the presence of biofilm, this technique is limited by its inability to provide speciation or antimicrobial susceptibility testing on the identified organisms [51,52].

Polymerase Chain Reaction (PCR)

We recommend against the routine use of nucleic acid-based testing for diagnostic testing for infection of the foot and ankle. In limited cases with high clinical suspicion of infection but negative cultures, PCR may help identify the unknown pathogens or antibiotic sensitivity. Although PCR techniques have proven to be more sensitive than traditional techniques, the number of false-positive results, as well as cost and availability of this technology, preclude routine screening. PCR should be reserved for limited cases with high clinical suspicion but negative cultures [53,54].

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QUESTION 3: What is the optimal method to perform bone biopsy (method, location, imaging use) for patients with foot and ankle infections?

RECOMMENDATION: A bone biopsy should generally be performed in a percutaneous fashion, particularly in cases where surgical debridement is not considered necessary.

If surgical debridement is considered necessary, then an open biopsy can be performed as part of the debridement.

Percutaneous biopsy should be performed under sterile conditions by an interventional radiologist or other physician trained in image-guided techniques.

The location of the biopsy will depend upon the clinical and radiographic evaluations, with a goal of maximizing the yield of the biopsy while minimizing the risk of injury to surrounding and/or overlying soft tissue structures.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

Infection in the foot and ankle bone or soft tissues can be associated with significant morbidity and even mortality. Prompt diagnosis and treatment are paramount. Often, diagnosis can be made based on a combination of clinical examination, radiographic imaging and laboratory data. Bone biopsy is considered the gold standard for the diagnosis of osteomyelitis [1–5].

Bone biopsy can be particularly helpful when the clinical exam, radiographic imaging and laboratory data are not clearly confirmatory of an underlying infection. Additionally, a bone biopsy can allow for identification of the infecting organism(s), and therefore allow for a more tailored treatment regimen. It can also exclude rarer causes of bone disease, such as malignancy or osteonecrosis [6,7].

A percutaneous bone biopsy is generally preferable to an open biopsy, particularly in cases where surgical debridement is not considered necessary. Percutaneous techniques are less invasive, less costly and are associated with less morbidity [7–10]. A percutaneous bone biopsy should be carried out under image guidance, generally either fluoroscopy or computed tomography (CT) and should be performed by an interventional radiologist or other physician trained on image-guided techniques. Image guidance allows for specimens to be obtained from specific targeted areas. The choice of imaging technique used to guide the biopsy depends on the anatomic location, availability and practitioner preference. Fluoroscopy can be used for more superficial lesions and allows for real-time guidance. Its main limitation is its two-dimensional nature. CT guidance provides visualization of not only osseous structures but also important soft tissue structures, such as neurovascular structures, within a three-dimensional framework. Its main limitation is the increased radiation exposure in comparison to fluoroscopy. There are reports in the literature regarding magnetic resonance (MR) guided percutaneous bone biopsies, but the availability of MRI-compatible instruments and accessories limits its use [11,12].

The choice of anatomical region to perform a biopsy will depend on the state of the overlying soft tissues and the radiographic findings. The goal should be to increase the yield of the biopsy while minimizing potential risk to nearby soft tissue structures. In general, more superficial areas of concern are targeted. If multiple areas of concern exist, one will also want to prioritize the site which is likely to provide the highest diagnostic yield. The procedure should be performed under sterile conditions to reduce the risk of contamination of skin flora. If possible, multiple samples should be obtained utilizing multiple trajectories within the bone to increase the diagnostic yield of the procedure.

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QUESTION 4: What is the best method to differentiate acute Charcot foot from acute infection?

RECOMMENDATION: Differentiation between acute Charcot neuroarthropathy (CN) and acute infection/osteomyelitis is complex and requires multiple (>1) diagnostic criteria. These criteria include an emphasis on the presence of neuropathy, history and physical examination. The absence of skin wounds and resolution of swelling/erythema with elevation makes the likelihood of infection very low.

In unclear cases, laboratory testing, histological examination and culturing of bone specimens, scintigraphy, and imaging, especially magnetic resonance imaging (MRI), may be of benefit.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

At initial presentation, acute infection comprising of cellulitis and osteomyelitis (OM) and CN may be difficult to differentiate. However, it is important for the clinician to make an accurate diagnosis, as correct treatment largely determines outcome as both present a substantial risk of limb amputation and mortality.

Physical features can provide essential clues to the diagnosis. The "probe-to-bone" test, which tests whether the underlying bone is palpable via a probe inserted into a wound, has demonstrated sensitivity ranging from 38 to 95%, specificity ranging from 84 to 98%, and a positive predictive value ranging from 53 to 97% for the diagnosis of osteomyelitis [1–6]. In their study of 1,666 consecutive diabetic patients, Lavery et al. demonstrated that a positive probe-to-bone test increases the probability of OM greater than 50%, whereas a negative test is a strong predictor of absence of infection [3]. The test, however, has shown to have a high variability when performed by inexperienced clinicians, but this intra-observer variability was demonstrated to decline with experience [7].

In terms of other physical features, CN typically affects the midfoot and lacks associated skin breakage, whereas OM is more frequently found in the forefoot and is often accompanied by soft tissue infection or ulcer [8,9]. Additionally, while it is possible to contract OM through hematogenous spread, the vast majority of cases are spread directly via a soft tissue infection or ulcer. A wound size > 4.5 cm^2 is associated with a three times higher chance of underlying OM [10]. However, others have suggested that both ulcers of size > 2 cm^2 and depth > 3 mm are also significant [11,12]. White blood cell (WBC) counts, C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR) are often utilized for work-up of infection. Some investigators have concluded that elevated ESR (> 70 mm/h) is strongly associated with OM [11–14].

A further benefit of ESR is that, while levels of the other inflammatory markers drop rapidly once antimicrobial treatment begins, ESR remains elevated for longer periods of time, therefore making it useful in monitoring treatment efficacy. Interleukin (IL)-6 has also been suggested as a marker for diagnosis of OM and monitoring treatment in preliminary studies [15,16]. However, these inflammatory markers are nonspecific and may be elevated by various other factors. Given that many patients with histologically proven OM may present with a normal WBC count, hematologic studies alone are not reliable for diagnosis of OM [11–14].

Bone culture alone is reported to have a sensitivity of 92% and a specificity of 60% in diagnosing OM in diabetic feet [17]. Bone samples can be obtained by percutaneous biopsy or during surgery [12,18]. However, bone specimens may often yield false-positive or false-negative results. Histologic analysis is suggested to be important in preventing these undesirable results, as several studies have shown that 40 to 60% of histologically proven cases of OM at surgery or biopsies of foot and ankle had negative cultures [19–22]. Therefore, standard criteria for the diagnosis of OM should be a positive culture with histopathologic evidence of infection in bone specimen [23].

Radiographic signs of infection, such as demineralization, periosteal reaction and cortical destruction, may not appear until two to three weeks after onset and require a loss of 40 to 50% bone mass to detect the difference [8,24]. The accuracy of plain radiography for early diagnosis is 50 to 60% with a sensitivity of 60% and a specificity of 80% [25,26]. Therefore, more advanced imaging is needed for diagnosis of acute osteomyelitis.

Magnetic resonance imaging (MRI) is suggested to be an effective modality to aid in early diagnosis [27,28]. A previous meta-analysis has shown that the sensitivity of MRI to diagnose OM in the foot and ankle is 90% sensitive and 79% specific [29]. In a meta-analysis of 16 studies, MRI performance was superior to that of technetium ^{99m}Tc bone scanning, plain radiography, and WBC studies. The sensitivity for the diagnosis of OM was found to be 90% while specificity was 85% [30]. MRI was better able to identify the extent of the involved area, whereas WBC bone scan may have better performance in differentiating OM from CN, especially in patients with metal implants [23,24].

While chronic CN shows low intensity in both T1- and T2-weighted images, both acute OM and acute CN show low signal on T1-weighted images and hyperintensity on T2-weighted images with contrast enhancement. However, these are common markers in both infective and neuropathic disease, making differentiation

of the two difficult [31]. OM almost always follows surrounding soft tissue infection, therefore identifying soft tissue edema, ulceration, or sinus tracts on imaging would suggest infection. MRI findings of diffuse bony edema in bony prominences (calcaneus, metatarsal heads, malleoli) and phalanges, with a contiguous spread would also suggest OM [32–34]. CN typically shows periarticular and subchondral changes (including fractures) as the pathology centers around the joint [35]. Disease affecting one or multiple joints, in particular of the midfoot, would also suggest CN [35].

Aside from MRI imaging, three-phase bone scintigraphy has a high sensitivity (80 to 100%) but poor specificity (25 to 60%) in diagnosing OM [36]. Labeled leukocyte scans (tagged WBC scans) are similarly sensitive, but more specific [23]. Capriotti et al. reported 86% sensitivity and 85% specificity for ^{99m}Tc-labelled leukocyte scintigraphy [37] and Dinh et al. reported that a ^{111}in-labelled leukocyte scan had a sensitivity of 74% and specificity of 68% [29]. Fluorodeoxyglucose (FDG) positron emission tomography (PET), which measures increased intracellular glucose metabolism, has demonstrated promise in diagnosing CN, particularly with regards to negative predictive value. Basu et al. found sensitivity and specificity of FDG PET in the diagnosis of CN to be 100% and 93.8%, both higher than the corresponding values of 76.9% and 75% for MRI [38]. Study results are inconclusive, however, with some authors finding that its use is limited when compared to MRI and WBC scintigraphy [39,40]. Further interesting developments in aiding in diagnosis are PET-computed tomography (CT) and PET-magnetic resonance (MR), which show promising early results [41–43]. Rastogi et al. reported the sensitivity and specificity of FDG PET-CT to be 83.3% and 100%, compared with 83.3% and 63.6% for contrast-enhanced MRI for the diagnosis of diabetic foot OM in the background of CN [41].

Previous systemic reviews of the literature (including the International Working Group on the Diabetic Foot's consensus scheme for the diagnosis of diabetic foot OM) and meta-analyses have proposed specific criteria for differentiation of CN from OM [21,23]. The proposal was based on using post-test probabilities to define broad levels of diagnostic certainty, with OM most likely being present if (1) a bone sample shows positive culture and is confirmed with histopathology, (2) intraoperative finding shows purulence in the bone, (3) intraosseous abscess is found on MRI or (4) exposed bone exists in the foot ulcer with corresponding changes in advanced imaging. However, the validity of the criteria has not been clinically tested and should, therefore, be utilized with caution.

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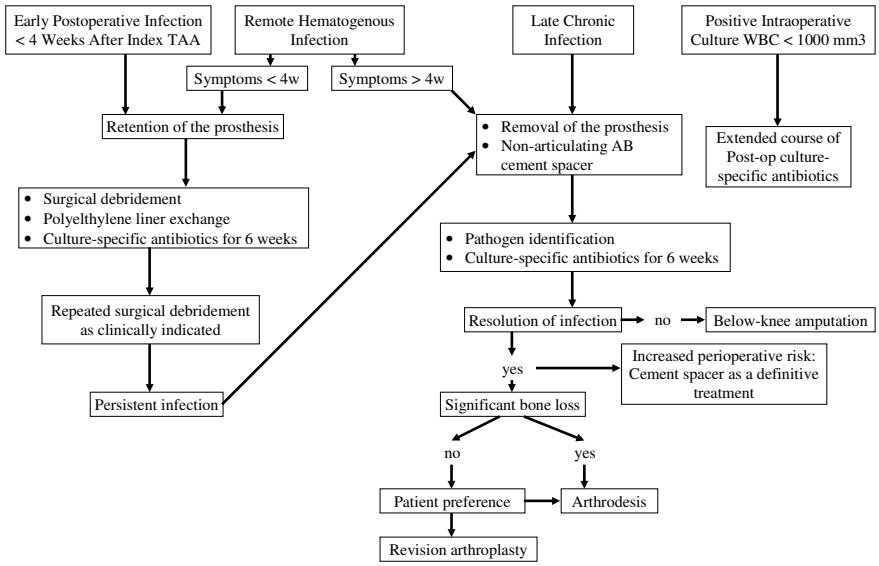
Treatment

3.1. TREATMENT: TOTAL ANKLE ARTHROPLASTY-SPECIFIC

Authors: Steven Raikin, Selene Parekh, Elizabeth McDonald

QUESTION 1: What is the treatment "algorithm" for an infected total ankle arthroplasty (TAA)?

RECOMMENDATION: The treatment of an infected TAA is largely dictated by the acuity of the infection. The following treatment algorithm modified for TAA is recommended [1].



LEVEL OF EVIDENCE: Limited

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

RATIONALE

The reported rate of infection after TAA is between 0 to 5% [2–4]. The management options are based on the time of presentation after index TAA and the duration of infection symptoms. It is a common practice to attempt to retain the ankle prosthesis when the infection is acute, particularly when it occurs during the early postoperative period. There are a number of treatment options available for infected TAA that includes surgical debridement, retention of the prosthesis and administration of intravenous antimicrobial therapy (DAIR), one or two-stage exchange arthroplasty, arthrodesis or amputation.

TAA infection literature cautions that great attention should be paid to delayed wound healing and its association with infection [5–10]. van der Heide et al. reported on the outcome of 58 TAAs in 51 patients with underlying rheumatoid arthritis (RA) or juvenile inflammatory arthritis (JIA) who had Buechel-Pappas or STAR implants [5]. Among this cohort, three patients (5%) developed early surgical site infection (SSI) and one of three (33%) patients treated with the van der Heide SSI protocol went on to develop a deep infection. The SSI protocol involved exploration of the surgical site, debridement of the wound and administration of systemic and local antibiotics. The ankle that developed deep infection underwent resection of the implant and subsequent fusion at six months. Further, Patton et al. reported on 29 cases of infected TAA and noted that 9 of the 29 (31%) infected TAAs were cases of delayed surgical wound healing that went on to deep infection [6].

Irrigation and debridement (I&D) can be a key first-step treatment of early TAA infections (early being defined as less than four weeks from the index TAA or remote hematogenous infection with symptoms less than four weeks) [7,11,12]. In a level III prognostic study, Kessler et al. defined infection parameters and proposed a treatment algorithm [7]. They selected 26 patients with PJI of TAA and matched patients with two control groups with 52 patients in each group. From this prognostic study, Kessler et al. proposed a diagnostic criteria for TAA infection which was based on presence of clinical

signs of pain, effusion, erythema and induration as well as one of the following criteria: (1) same microorganism growth in two or more cultures of synovial fluid and/or periprosthetic tissue, (2) visible pus surrounding the joint, (3) acute inflammation upon histopathological examination (greater than or equal to 10 neutrophils/high-power field) or (4) the potential to probe the base of a wound at the implant. They defined exogenous cases as locally acquired through the wound and hematogenous cases had an uneventful postoperative course for a minimum of *three months* after the initial TAA and/or there was a distant infection source. Four of 26 (15%) TAA infections were hematogenous in origin, and 22 of 26 (85%) TAA infections were exogenous. Meanwhile, *Staphylococcus aureus* and then coagulase-negative staphylococci were the most common pathogens. When compared to the control, risk factors for developing deep infection included persistent wound dehiscence (odds ratio (OR) = 15.38, 95% confidence interval (CI) = 2.91 to 81.34, p = 0.01, in comparison with both control groups) and secondary wound drainage (OR = 7.00, 95% CI = 1.45 to 33.70 in comparison with the age/sex-matched group and OR = 5.31, 95% CI = 1.01 to 26.78 in comparison with the time-matched group, p £ 0.04).

The TAA literature reports upon the success of irrigation and debridement (I&D) in early postoperative cases. Mann et al. reported on 84 ankles in 80 patients with a mean follow-up of 9.1 years with a 3 in 84 (3.5%) incidence of deep infection [10]. All deep infections were exogenous and occurred immediately postoperatively as a result of incomplete wound healing. Mann et al. treated all deep infections with open debridement and six weeks of intravenous antibiotics. One of the deep infections required a local skin graft and another required a free vascularized tissue flap for closure. No metallic prostheses were removed and there was no evidence of recurrent infection with an average follow-up of 9.3 years [10]. These results demonstrate the success of early debridement. Further demonstrating the success of I&D amongst exogenous cases, Nodzo et al. reported on 75 ankles with Salto Talaris prostheses. One of the 75 (1.3%) went on to develop deep infection within the first three weeks following TAA [11]. The patient was treated with I&D and intravenous antibiotics and the patient retained all components. Similarly, Borenstein et al. reported one ankle out of 65 consecutive TAAs (1.5%) that experienced deep infection [12]. The patient was treated with I&D and six weeks of intravenous antibiotics. Additionally, Patton et al. demonstrated the merits of I&D in detailing 29 cases of infected TAA [6]. If an I&D and revision arthroplasty were performed, 23 of 29 (79%) limbs were salvaged. Meanwhile, if revision TAA alone was performed, 19 of 29 (65%) TAA retention was reported.

In addition to I&D, the literature details the effectiveness of polyethylene liner exchange in cases of early postoperative infection and remote hematogenous infection when symptoms extend for less than four weeks [14–17]. Claridge et al. responded to the 2 of 28 (7%) cases of deep infection with polyethylene exchange only [13]. Similarly, Stoodley et al. detailed polyethylene liner exchange as an important early treatment step [16].

Reports on revision TAA after deep infection are variable [15,16,18–21]. In a case report describing TAA infection after a routine dental procedure, Young et al. described the work-up, blood cultures positive for *Streptococcus mitis* and a 6-week course of antibiotics with penicillin G and 18 million units intravenously daily for one additional week [17]. The patient remained non-weightbearing in a CAM boot until revision TAA surgery at three-months post-infection. Good outcomes with the patient walking pain-free at 16-month follow-ups were recorded. While Sproule et al. also opted for a revision TAA to treat the 1 of 88 (1%) for deep infection, they opted for a two-stage revision and recounted successful results [18]. Further reports of metal component revision after deep infection TAA demonstrated good results [15,19].

In a retrospective case series on 613 TAA, the 19 cases of deep infection were treated by established algorithms depending on if they were exogenous or late chronic infection [14]. For exogenous infection, Myerson et al. attempted prosthesis retention for 4 of 19 (21%) implants. Three (16%) had early post-op infections at three, five and seven weeks following initial implantation. All had I&D plus polyethylene liner exchange and later antibiotic therapy. One (5%) had an acute hematogenous infection. In this strategy, all four patients had recurrent infection and went on to require removal of the implant and staged treatment. Meanwhile, 15 of 19 (79%) deep infections in this series were late chronic infections. Of the deep infections, seven revision TAA were attempted but only three (16%) were successful. Of the four that failed revision TAA, three had recurrent infection and one aseptic loosening. Otherwise, for successful revision surgery, six patients were converted to arthrodesis; seven patients had a permanent antibiotic spacer, and three patients underwent transtibial amputation. The mean time to revision TAA or arthrodesis following initial infection treatment was 7.8 months (range, 2.5 to 13 months).

Revision TAA after late chronic infection has no consensus, and others advocate for conversion to arthrodesis in the case of infected TAA [8,15,22–25]. As reported by Myerson et al., six patients converted to arthrodesis all had successful revision, but only three of seven (43%) TAA revisions were successful [14]. Additionally, McCoy et al. reported on three failed TAAs due to infection [22]. These patients were revised using circular external fixator-assisted ankle arthrodesis and distraction osteogenesis for limb length equalization. All patients reported solid pain-free fusion and good subtalar joint alignment. Further evidence of good results, Mulhern et al. recounted the successful conversion to tibiotalocalcaneal arthrodesis with custom titanium alloy truss and retrograde intramedullary nail after revision TAA polyethylene became infected with *Staphylococcus aureus* [23]. Devries et al. added evidence to support arthrodesis instead of revision TAA after infection [24]. In their case series of five revision TAAs, Devries et al. initially converted the one deep infection directly to a revision TAA. While the deep infection was cleared at the time of replacement, the revision TAA went on to develop an infection. After failing two courses of long-term IV antibiotics, an antibiotic spacer was implanted and later converted to a tibiotalocalcaneal arthrodesis.

However, if deciding to proceed with a revision TAA after deep infection, there is evidence to support that single hydroxyapatite component coating should not be used in the revision [25]. When examining 117 consecutive ankles in which TAA failed after mean 4.3 years, Hinterman et al. found that 9 of 117 (8%) TAAs failed due to infection [26]. Avoiding single hydroxyapatite component coating, the group reported that the custom long-stemmed talar implant had good results amongst revisions with a 100 in 117 (85%) success rate, and one revision TAA attributed to deep infection.

While wound closure for deep infection is a coordinated effort with plastic surgery, plastics' perspective on wound closure for infected TAA is valuable when discussing a TAA infection algorithm. Goldstein et al. reported on two infected TAA treated for random local flap for wound coverage of the ankle [9]. Patients presented at a wound healing center for random local flap for wound coverage of the ankle. "Patient 3" required two flaps for infected TAA with lateral ankle wound: one peroneus longus muscle flap with hardware as exposed structure and one fasciocutaneous transposition flap with fibula as the exposed structure. "Patient 3" required 4 total operations and had a 55-day follow-up with no resultant complications. Meanwhile, "Patient 9" required two flaps for infected TAA with lateral ankle wound: one lateral calcaneal artery fasciocutaneous flap with hardware as the exposed structure and one fasciocutaneous transposition flap with hardware as the exposed structure. "Patient

9" required 2 total operations and had a 75-day follow-up with no resultant complications.

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QUESTION 2: What is the optimal (type, dose and route of administration) antibiotic treatment for patients with infected total ankle arthroplasty (TAA)?

RECOMMENDATION: Though literature specific to TAA is lacking, based on recommendations for the management of hip and knee arthroplasties, the choice of antibiotic should be made based on the identification and sensitivities of the infecting organism(s). Dosing, frequency and route of administration of antibiotics may be determined in consultation with an infectious disease specialist and by taking into account the patient's weight and comorbidities, such as renal impairment and the antibiogram.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

There is a paucity of literature regarding the treatment and outcomes of periprosthetic joint infection (PJI) in TAA. The two largest studies on post-TAA infection from the United States report the use of six weeks of intravenous (IV) antibiotic therapy following surgical treatment of the infection [1,2]. In a study from Europe, Kessler et al. reported the use of one to two weeks of IV antibiotics followed by three months of oral antibiotics following surgical treatment for infection [3]. In all of these studies, the choice of antibiotic(s) was made based on the identified infecting organism(s) and its antibiotic sensitivity and with the assistance of an infectious disease specialist. In general, the most common pathogens responsible for PJI are *Staphylococcus aureus* (methicillin-susceptible or -resistant), coagulase-negative Staphylococci and other constituents of the skin's bacterial flora [4,5].

The timing of PJI following TAA is also important in determining infection management. If the infection developed within 6-12 weeks of implantation, this is considered an acute infection and debridement with retention of the implants (DAIR) and antimicrobial treatment are the most desirable approach. Conversely, for a device that has been present for more than three months, a chronic infection is presumed to be present, and a one- or two-stage exchange with antimicrobial treatment is the desired course of action [5–7].

In the hip and knee literature, there has been a debate with regards to the duration of antibiotic treatment. Some studies have recommended as many as three to six months of antimicrobial therapy following surgical intervention, depending on the organism [6,8]. However, other studies have shown six weeks of IV antibiotics to be a sufficient duration of treatment [9–11].

The theoretical benefit of a shorter course of antibiotics, aside from patient convenience, includes a reduced risk of adverse drug events (ADEs), including anaphylaxis, nephrotoxicity, hepatotoxicity and infectious colitis, as well as bacterial resistance [12]. The International Consensus on Periprosthetic Joint Infection stated that the duration of antibiotic therapy following removal of implants is inconclusive but recommended a period of antibiotic therapy between two to six weeks [13].

The authors of the Infectious Diseases Society of America (IDSA) Guidelines for the Diagnosis and Management of Prosthetic Joint Infection make the following recommendations for the management of hip and knee arthroplasties while suggesting that similar recommendations can be extended for the management of TAA infections [6]. The IDSA recommends four to six weeks of pathogen-specific IV or highly bioavailable oral antibiotic therapy following removal of implants, regardless of organism or in non-staphylococcal PJI treated with DAIR. They recommend two to six weeks of IV antibiotics in combination with oral rifampin, followed by 3 months of rifampin plus a companion oral antibiotic for a staphylococcal TAA PJI treated with DAIR. If rifampin cannot be used because of an allergy or toxicity concern, the IDSA recommends four to six weeks of IV antibiotic therapy. Of note, the IDSA recommendations are the same in the setting of a one-stage exchange as they are following DAIR [6].

Further studies on the treatment and outcomes of infection in TAA are needed. For now, we must rely on the hip and knee arthroplasty literature as well as the recommendations of the MSIS and IDSA.

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QUESTION 3: Is there a role for suppressive antibiotics in patients with perioperative joint infection (PJI) of total ankle arthroplasty (TAA) who have undergone surgical treatment?

RECOMMENDATION: Culture-directed antibiotic therapy is recommended for patients undergoing surgical treatment of infected TAA. Routine administration of suppressive antibiotics in patients with an ankle prosthesis in place is not warranted; however, in certain clinical circumstances, this may be of benefit.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

There is scant literature related to the management of infected TAA. The available reports have been reviewed to determine if there is a role for routine administration of suppressive antibiotics after surgical management of infected TAA. The published studies do not address the issues of suppressive antibiotic therapy after infected TAA.

Myerson et al. reported on 19 patients with infected TAA [1]. In early acute infections, patients were treated surgically with irrigation and debridement (I&D) and polyethylene exchange, followed by six weeks of antibiotics. Of the four patients treated with this approach, all had persistent infections and required prosthesis removal. No comment was made regarding suppressive antibiotics after staged revision for infection. Patton et al. reported on a series of 29 TAA infections [2]. Acute infections were treated with polyethylene exchange and I&D. Of 14 acute infections, only three were treated successfully with this approach. Again, no comment was made regarding suppressive antibiotics after staged revision.

There is also little related to this question in the hip and knee literature. A recent study supported by The Knee Society evaluating this issue after surgical management of infected TAA found that

administration of suppressive antibiotics after reimplantation of the knee in patients undergoing two-stage exchange arthroplasty resulted in lowering the rate of subsequent failure [3]. The authors of the study stated that the findings were preliminary and further long-term data on the cohort was needed.

There are many potential issues related to administration of routine suppressive antibiotic therapy after surgical management of infected prosthetic joints. Cost, the potential for emergence of antimicrobial resistance, systemic adverse effects and so on are some of these potential issues. Therefore, and in the absence of concrete data, we believe that routine administration of suppressive antibiotic therapy for patients with a prosthetic ankle joint in place is not warranted. We realize that patients with infected TAA need to be treated on an individual basis and administration of oral antibiotics to some patients, such as those with extensive comorbidities, those infected with resistant organisms and those with complex infections may be justified in some circumstances.

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QUESTION 4: What determines the type and dose of antibiotic that is needed to be added to the cement spacer in patients with infected total ankle arthroplasty (TAA)?

RECOMMENDATION: We recommend tailoring the antibiotic in cement spacers to the infecting organism if it has been identified, as is typically done in total knee and hip arthroplasty. Otherwise, broad-spectrum antibiotics may be utilized. Medical comorbidities should always be considered, especially with regard to renal function and allergy profile. A thermostable antibiotic should be added to cement.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

TAA is performed much less frequently than total hip and knee arthroplasty, and reports related to deep infections and associated management are limited.

Like hip and knee arthroplasty, management of infected TAA may include removal of prosthesis and insertion of an antibiotic-impregnated cement spacer. An antibiotic spacer, as part of two-stage exchange arthroplasty, has been utilized in the management of infected TAA. Lee et al. described the use of cement mixed with 1 gm gentamicin, 1 gm vancomycin and 1 gm cefazolin in nine patients with infected ankle joints, three of whom were status post TAA [1]. The infecting organisms of the three TAA patients included methicillin-resistant *S. aureus* (MRSA), methicillin-resistant *S. epidermidis* (MRSE) and *Enterococcus*. The authors utilized their technique with the intent of permanent spacer use and a return to weightbearing, as multiple lower extremity operations have been associated with amputation.

Given the fragile soft tissue envelope around the ankle, Ferrao et al. also describe the use of a definitive antibiotic spacer after ankle infection [2]. Six of nine patients were status post-TAA and required explantation due to infection. The authors indicated that culture-specific antibiotics were mixed into cement when possible, although the detailed combination was not listed. If the infecting organisms were not isolated by culture, 2 gm vancomycin and 1.9 gm gentamicin were mixed into the cement. Bacteria were isolated in seven of the nine patients: *Staphylococcus aureus* (n = 3), *Staphylococcus epidermidis* (n = 3) and *Streptococcus viridans* (n = 1). Three patients required additional surgery, including two patients who underwent below-the-knee amputations.

In a large series including 966 patients, 29 patients were identified with infection after primary or revision TAA [3]. Cement spacers were placed in 17 cases, although the antibiotic formulation of the spacers was not indicated. The most common infecting organisms included methicillin-sensitive *S. aureus* (MSSA), coagulase-negative staphylococci and polymicrobial infection (one of which included MRSA).

Fifteen deep infections were identified in another series including 613 primary and revision TAAs at a single institution [4]. An additional four deep TAA infections from outside facilities were also treated during the study period. Antibiotic spacers formulated with 1 gm vancomycin and 1.2 gm tobramycin per cement packet were used for chronic infections requiring explantation. The infecting organisms included coagulase-negative Staphylococcus (n = 6), MSSA (n = 4), MRSA (n = 2), *C. acnes* + coagulase-negative Staphylococcus (n = 1), *E. coli* (n = 1), *S. viridans* (n = 1) and polymicrobial including MRSA (n = 1). Four attempted reimplantations were performed, but all subsequently failed due to infection with coagulase-negative Staphylococcus and MSSA.

Another study documented 26 TAA infections in a cohort of 408 patients at a single institution [5]. The most common infecting organisms included *S. aureus* (n = 8), coagulase-negative Staphylococcus (n = 8), *Enterococcus* (n = 4), polymicrobial (n = 4), *Enterobacter* (n = 3), *Klebsiella* (n = 2), *C. acnes* (n = 2) and MRSA (n = 1).

If the infecting organism is known prior to explantation based on preoperative aspiration, the use of tailored antibiotics incorporated into the cement spacer is recommended [3]. This has been recommended in total hip and knee replacement and can be extrapolated for use in the ankle [6,7]. Antibiotic-laden spacers result in higher antibiotic concentration at the infected site for a longer duration than that achieved with systemic antibiotics alone [8]. Tailoring the antibiotic selection is important to avoid breeding unneces-

sary resistance that has been identified after aminoglycoside-impregnated spacers [9].

Antibiotic selection requires consideration of a number of factors. Cultures from preoperative aspiration are informative; however, draining sinus cultures may have contaminating organisms [8,10,11]. Consultation with a microbiologist or infectious disease service may be helpful to determine an appropriate preparation for the cement spacer [12]. If no organism is identified, antibiotics with broad-spectrum coverage may be utilized [6,8,13,14]. One study showed effective eradication of infection with the use of 2 gm vancomycin, 2 gm gentamicin and 2 gm cefotaxime per 40 gm packet of cement for broad-spectrum coverage [7]. This combination is effective against MRSA (vancomycin), gram-negative bacteria including Pseudomonas (gentamicin) and gentamicin-resistant organisms (cefotaxime) [15].

When selecting an appropriate antibiotic profile for the cement spacer, factors to consider include thermostability, water solubility, patient allergy and availability as a sterile powder [7,16]. Some of the available options include gentamycin, vancomycin, ampicillin, clindamycin, tobramycin and meropenem [7,12,17]. Tobramycin is commonly used and has been shown to be stable during the exothermic reaction of cement mixing and elutes in high concentration to be effective against multiple common bacteria implicated in periprosthetic joint infection [18].

Combining antibiotics may result in higher local antibiotic concentration than individual antibiotics. Vancomycin combined with imipenem-cilastatin eluted higher concentrations of antibiotic and for a longer duration when compared to in vitro elution of vancomycin-impregnated cement alone [19]. Similar findings have been shown with vancomycin combined with tobramycin [20]. Tobramycin also has been shown to elute in higher concentration and for a longer duration than vancomycin [21]. Tobramycin, gentamicin and vancomycin are the most commonly used antibiotics, but others have been described and may be utilized depending on patient allergy profile, bacterial resistance and fungal infection [22].

The additive effect seen with certain antibiotics may be related to the higher solvent concentration in the cement that can diminish structural integrity but increase surface area for elution. To that effect, mixing the cement and antibiotic without vacuum assistance is theoretically superior since porosity is increased [23]. Palacos (Heraus; Wehrheim, Germany) cement seems to have a better profile for use than Simplex (Stryker; Mahwah, NJ) cement in multiple studies that show antibiotic elution in higher concentrations and for a longer duration [21,24–26]. In general, mixing more than 5 gm of additional powdered antibiotics into cement is not recommended because of its effect on the mechanical strength of the cement and potential for systemic toxicity [27]. Some antibiotics, such as rifampin, have been shown to interfere with cement curing and may not be ideal for use [28]. However, new technology with alternative delivery systems, like rifampin in microencapsulating in alginate beads, may allow broader coverage of infecting organisms as greater rates of antibiotic resistance emerge [28].

Common doses of antibiotics added to cement for treatment of periprosthetic joint infection are shown in Table 1. There are a wide variety of published quantities of antibiotics, with the trend generally going towards higher doses. However, a recent study demonstrated that higher dose antibiotics are not necessarily associated with the best elution properties; optimal in vitro antibiotic dosage in terms of elution rate and duration included tobramycin 3 gm and vancomycin 2 gm [29]. Vancomycin 2 gm per 40 gm packet of cement has been shown to meet the minimum inhibitory concentration (MIC) for five weeks after implantation [19,23]. Some antibiotics such as cefazolin, ciprofloxacin and ticarcillin, do not maintain adequate elution levels and are therefore less favorable for use [30].

TABLE 1. Antibiotic additives to cement for treatment of periprosthetic joint infections

Antibiotic	Activity Against	Quantity per 40g Cement Packet	Notes
Vancomycin-P	Gram-positive bacteria including methicillin-resistant organisms	2 gm [19,23]	
		4 gm	Studied in combination with ceftazidime 4 gm for broad-spectrum coverage [45]
Tobramycin	Gram-negative bacteria including *Pseudomonas*	2.4 gm [46]	
		4.8 gm [47]	
Daptomycin	Gram-negative bacteria	1 gm [25]	
Amikacin	Gram-negative bacteria and *staphylococcus*	1 gm [25]	
Clindamycin	Gram-positive cocci and anaerobes	6 gm [30]	
Imipenem/Cilastatin	Broad spectrum including gram-positive and gram-negative including *Pseudomonas* and *Enterococcus*	2 gm	Studied in combination with vancomycin 2 gm [19]
Ceftazidime	Gram-negative bacteria including *Pseudomonas*	4 gm	Studied in combination with vancomycin 4 gm for broad-spectrum coverage [45]
Amphotericin B	Fungal infections	100-150 mg [48]	

During the addition of antibiotics to cement, drug metabolism and concentration should also be considered. In addition, the medical comorbidities of the patient, such as renal function and allergy profile, should be considered, as these will influence the dose of antibiotics to be added to the cement and may preclude certain classes of antibiotics to be used. The incidence of acute kidney injury due to elution of antibiotics from a cement spacer has been reported to range between 4.8 and 20%, as aminoglycosides and vancomycin are both renally excreted [7,31–34]. Furthermore, a high concentration of certain antibiotics may be detrimental to local tissues and affect healing. Tobramycin can decrease cell growth if the concentration is greater than 400 micrograms/mL [35]. Gentamicin levels greater than 100 micrograms/mL have cytotoxic effects on osteoblasts, and this threshold is commonly exceeded for ten days after implantation of a spacer with gentamicin [36–38]. Vancomycin appears to be safe as long as the concentration is under 1,000 micrograms/mL [39].

Because of the risk of bacterial contamination may increase with time, the duration of an antibiotic spacer in situ should be limited. This is especially true if revision TAA is planned. The spacer may become colonized in 15 to 50% of cases, and the odds ratio of reinfection when positive culture is obtained from a cement spacer is eight times [40]. Recently, resistant bacteria have been identified on antibiotic-cement beads at the time of reoperation [41]. The antibiotic elution decreases over time, which reaffirms limiting the duration of spacer use [40,42–48].

Based on our understanding of the available literature, including much related to management of infected hip and knee arthroplasties, we recommend that 2 gm of vancomycin and 2.4 gm of tobramycin be mixed with every packet (40 gm) of methylmethacrylate cement to allow for coverage of a broad spectrum of organisms. In some infected TAA cases, additional or alternative antibiotics may be needed based on the identity of the infecting organism(s) and the antibiogram. Unless used as definitive treatment, the cement spacer should not be left in situ for too long because of the potential for the spacer to act as foreign material after antibiotic elution is completed (usually within a few weeks).

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QUESTION 5: What are the indications and contraindications for irrigation and debridement and retention of prosthesis (DAIR) in patients with infected total ankle arthroplasty (TAA)?

RECOMMENDATION: DAIR with polyethylene exchange may be indicated in early postoperative infection (< four weeks) or acute hematogenous infection (< four weeks of symptoms) in patients with infected TAA, although recurrent infection has been seen. Sufficient clinical evidence is lacking.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

Periprosthetic joint infection (PJI) is a serious complication after TAA. Deep infection of TAA can be limb-threatening; hence, prompt treatment is required to minimize the potentially devastating effects of infection. Currently reported infection rates after TAA range from 1.1 to 8.5%, with reports indicating that newer anatomic designs have lower overall infection rates [1–6].

The current indications for DAIR in infected TAA include early postoperative infection and acute hematogenous infection. Myerson et al. retrospectively reviewed 572 TAAs over a 10-year period and found 19 cases of PJI (3.3%), including 15 chronic infections, three early postoperative infections, and one acute hematogenous infection [7]. The three early postoperative infections and one acute hematogenous infection were treated with initial irrigation and debridement with polyethylene liner exchange. All four cases resulted in recurrent infections that were treated with successful revision TAA, tibiolacalcaneal fusion and antibiotic cement spacer with an average retention time of six months. Only one case had an initial negative culture. The authors postulated that the inability to eradicate bacteria could be secondary to the ankle's unique anatomy with difficult access to regions such as the posterior gutters to perform a complete debridement. Additionally, Patton et al. reviewed 966 TAA over a 17-year period and found 29 cases of infected TAA (3.2%) [8]. They treated acute infections with polyethylene exchange in two cases and debridement alone in three cases. All five cases were apparently treated successfully with no evidence of subsequent failure.

There is paucity in the current literature regarding the management of PJI of TAA. Indications for DAIR are limited to early postoperative infection and acute hematogenous infection, and most guidelines are derived from the knee and hip studies. There are mixed results even in this selected group of patients, as all four patients with early infection from one study suffered persistent infection following DAIR, raising questions regarding the efficacy of this procedure. It is unclear at this point whether the failures stem from inadequate debridement due to the unique anatomy of the ankle or whether the natural history of ankle infection is inherently different than that of the hip and knee. Larger and additional studies are needed to provide a higher level of recommendation at this point.

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QUESTION 6: What is the optimal protocol for performing debridement, antibiotics and implant retention (DAIR) in an infected total ankle arthroplasty (TAA) (type and volume of irrigation solution, and so on)?

RECOMMENDATION: DAIR in acute TAA infections may be an acceptable treatment option. If performed, DAIR should be done meticulously, ensuring that all necrotic or infected tissues are removed and modular parts of the prosthesis, if any, exchanged. The infected joint should also be irrigated with antiseptic solutions.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

For total hip and knee periprosthetic joint infection (PJI), the DAIR procedure is a viable alternative to explantation or one-stage revision in cases of early infections by a relatively antibiotic-susceptible bacteria, in the absence of mechanical problems or a sinus tract. Concerning TAA infections, these general prerequisites for DAIR are not different than for other PJIs, but the success of DAIR in TAA infection is relatively poor (see Table 1). The best evidence is reported by Kessler et al. [1]. The authors investigated 34 cases of TAA infection, of which 21 were treated by DAIR. Remission using the DAIR procedure was achieved only in two-thirds of all cases (14 of 21, 67%) [1].

The reason for failure of DAIR in hip and knee PJI cases has been linked to resistance of bacteria, poor host and inability to remove modular components, which would then compromise the ability to perform meticulous debridement. Most surgeons will agree that the aforementioned factors are important ones influencing the outcome of DAIR. They will also posit that one of the most important metrics governing the success of DAIR is the method used by the surgeon to perform the procedure. Meticulous debridement and the use of copious antiseptic solutions are all believed to be an important part of bioburden reduction, which in turn affects the outcome of this procedure [4–6]. When DAIR is attempted, available literature infrequently gives in-depth insight into the surgical details – approach, volume and type of irrigation solution or, perhaps most importantly, the frequency of poly exchange versus retention.

Practically, the anterior approach is most commonly described [1–3] and poly-exchange frequently endorsed [3,4]. The duration of concomitant antibiotic prescription is most commonly six weeks of therapy (most commonly intravenous); however not all routes of administration or duration is conveyed in the literature reviewed [1–4,6]. The use of vacuum-assisted devices is not reported in the treatment of TAA infections, rather in the promotion of wound healing and the prevention of infection after primary elective arthroplasty [7,8].

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TABLE 1. Investigation of 34 cases of TAA infection

Author	Number of TAA Infections	Number of Attempted DAIR	Remission
Kessler et al. [1]	34	21	14/21 (67%)
Ferrao et al. [2]	6	0	6/6 (100%)
Myerson et al. [3]	19	4	All DAIR patients developed later infection and failed
Patton et al. [4]	29	5	Unknown for DAIR

TAA, total ankle arthroplasty; DAIR, debridement, antibiotics and implant retention

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QUESTION 7: What are the indications for one-stage versus two-stage exchange arthroplasty in management of the infected total ankle arthroplasty (TAA)?

RECOMMENDATION: Two-stage exchange arthroplasty is recommended in the majority of cases following infected TAA. One-stage arthroplasty is only indicated in a limited patient population with acute infection, preoperatively identified low-virulence organisms and low-risk patient factors.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 92%, Disagree: 8%, Abstain: 0% (Super Majority, Strong Consensus)

RATIONALE

The management of the infected arthroplasty remains a challenging and controversial topic in relation to any joint [1–5]. Reported rates of infection following TAA requiring re-operation (surgical irrigation and debridement (I&D), component removal and exchange, or revision) range from 0 to 8.6% [6–11]. Special consideration must be taken into account in the management of the infected total ankle given the tenuous soft tissue coverage, frequent history of multiple preceding operations, and, relative to hip and knee arthroplasty, a more recent arthroplasty design and more limited experience [12]. Currently, two-stage revision exchange arthroplasty surgery is the most popular surgical option for the management of periprosthetic joint infection (PJI) in North America and worldwide. However, it may result in significant bone loss, patient morbidity and prolonged disability, leading to a more challenging reconstruction and ultimately prolonged recovery, poorer patient-reported clinical functional outcomes, higher rates and risk of subsequent infection and potential failure of salvage operations leading to amputation.

Surgical treatment goals of the infected TAA are to eradicate the infection, obtain mechanical stability and soft-tissue coverage, alleviate pain and maximize clinical function. Historic treatment strategies have included antibiotics with hardware retention, aggressive debridement with or without polyethylene exchange and removal of hardware and exchange or arthrodesis in one or two stages with an antibiotic-impregnated cement spacer.

Extreme care should be taken when considering appropriate management of the infected TAA. Kessler et al. published the largest study to date evaluating 34 patients following revision TAA for infection [10]. An infection-free outcome with satisfactory function of the ankle was obtained in only 23 patients (67.6%). One-stage revisions with retention of one or both components resulted in 33.3% (7/21) failure with persistent infection, whereas two-stage revision with explantation of all components results in 10% (1/10) failure. Myerson et al. retrospectively evaluated 19 revision cases, and only 3 of the 19 patients underwent successful revision with replacement (15.7%), 6 with arthrodesis (31.6%), 7 with a permanent antibiotic spacer (36.8%) and 3 patients required a transtibial amputation (15.7%) [11]. Although prosthesis salvage was attempted in three early postoperative and one acute hematogenous cases, all revision cases ultimately required subsequent removal of the prosthesis. Whereas Myerson et al. reported that no patient was successfully treated with retention of the hardware, Patton reported conflicting results with four of four patients (100%) successfully treated with retention of hardware and irrigation and debridement (two with and two without exchange of polyethylene liner) for heterogeneous presentations (one acute presentations with cellulitis, one acute presentation with dehiscence, one late chronic, and one remote hematogenous) [12]. However, the majority of the patients in this study were treated with two-stage revision arthroplasty or amputation with retention of arthroplasty only achieved in 19 (65%) cases of infection (n = 29). Given the currently available literature, there are conflicting data for the utility of surgical I&D with retention of hardware. Future studies are necessary to evaluate the feasibility of surgical I&D of PJI in TAA.

To date, there is no level I evidence that provides indications or contraindications for a one-stage exchange arthroplasty in TAA. Furthermore, there are no randomized controlled trials that provide absolute indications or contraindications for two-stage exchange arthroplasty in hip and knee arthroplasty [13–16]. Care must be taken to determine the need for implant removal given that the reported success of treating the infected TAA with retention of one or both implants ranges from 0 to 100% [7,11,12]. Given the variability in the reported rates of success in eradicating infection, morbidity and mortality among observed patient populations and variable time periods prior to reimplantation, direct comparisons with one-stage exchange arthroplasty are difficult due to a patient selection bias in the current literature [15–18]. Although no literature is available with respect to TAA, a recent systematic review of the knee arthroplasty literature by Romano et al. demonstrated that a two-stage exchange provides, on average, a better outcome with respect to the control of infection in the knee [19]. The same group recently presented similar but less notable findings for the hip [20]. It is not clear how these findings would translate to the ankle, and future studies are necessary to better understand the potential for infection control and functional outcome with one- versus two-stage revision arthroplasty.

There are, however, circumstances that necessitate the removal of implants. Systemic infection necessitates timely administration of appropriate antibiotics and prompts removal of implants with thorough debridement of the soft tissues and bone in order to address the potential life-threatening sequelae of PJI. The immunocompromised patient or the presence of medical comorbidities, including metastatic disease, advanced cardiac disease and renal and/or liver dysfunction, have been shown to impact the rate of success for infection eradication and certainly influence morbidity and mortality [7,10]. It is unknown if the presence of these comorbidities constitutes a contraindication for one-stage exchange arthroplasty in TAA [14–16,18,21,22].

Since 1999, when Costerton first attributed the persistence of certain chronic infections to the presence of biofilm, the majority of implant-related infections in orthopaedics are believed to be secondary to biofilm-related infections [23]. These infections are associated with glycocalyx polysaccharide biofilms that pose unique challenges including frequently being recalcitrant to antibiotic treatment and may be culture-negative with ineffective clearance from the host [24,25]. Failure to identify the offending organism and/or culture-negative PJI is a relative contraindication to one-stage exchange arthroplasty [13,16,26,27]. Given the risk of biofilm-related

TABLE 1. Indications for one- versus two-stage exchange for infected TAA

Treatment Type	Indications
One-stage Exchange Arthroplasty	No sinus tract or exposed hardware Healthy patient and soft tissue No prolonged antibiotic use No significant bone loss requiring bone graft Low-virulence Organism with good antibiotic sensitivity
Two-stage Exchange Arthroplasty	**Sepsis.** Patients with systemic manifestations of infection **No Cultured Organism.** High suspicion for infection but no organism has been identified **Antibiotic-resistant Organism.** Preoperative cultures identifying difficult to treat and antibiotic-resistant organisms **High-risk Patient Factors.** a. Presence of a sinus tract or exposed hardware b. Immunocompromised c. Inadequate and non-viable soft tissue coverage d. Need to utilize higher order reconstructive techniques (bone graft, augmentation, soft-tissue flaps)

TAA, total ankle arthroplasty

infections, several authors advocate that reimplantation of a prosthesis should be delayed until adequate resuscitation and eradication of the offending organism have been confirmed [13–16,21,26–31].

The presence of compromised soft tissues (e.g., sinus tract, exposed hardware, etc.) that may limit adequate implant coverage is another indication for two-stage exchange arthroplasty. Sinus tracts frequently present with indurated, poorly elastic surrounding tissue near and around the ankle that limits the potential for adequate primary closure. In addition, the presence of a sinus tract may contaminate preoperative cultures and preclude the prerequisite for the identification of the offending organism [4,13,16,26,27]. Tissue expanders, musculocutaneous flaps and possible repeat debridements may all be indicated, necessitating further time between initial resection and reimplantation [14–16,22]. If soft tissue coverage cannot be obtained at index revision of a one-stage exchange arthroplasty, a two-stage surgery should be considered [13–15].

If the decision is made to pursue two-stage arthroplasty, there is no definitive evidence in the literature concerning the optimal timing between the two stages. However, there should be ample time to allow administration of a complete full course of antibiotics, eradication of the offending organism supported by a decrease in inflammatory markers (C-reactive protein [CRP]/erythrocyte sedimentation rate [ESR]), and adequate soft tissue preparation. Although no literature exists demonstrating the optimal timing of replantation in TAA, there is evidence that replantation prior to completing a complete six-week course of antibiotics may result in increased positive cultures at the time of surgery in the hip and knee [14,16]. In the United States, the most common practice is to complete a course of six weeks of intravenous or oral antibiotics followed by a cessation of antibiotics for two to eight weeks prior to reimplantation [16,32,33]. In addition, in the adult hip arthroplasty literature, there is evidence that delaying replantation beyond six months impairs functional improvement compared to patients who underwent two-stage exchange within six months of resection and reimplantation [34]. Although we recommend trending the ESR and CRP, the need for serologic evaluation prior to reimplantation is unclear. Although ESR and CRP alone are poorly diagnostic of persistent PJI with no optimal cutoff values, changes in inflammatory marker values from the time of resection may demonstrate improved pathogen control and decreased overall biologic burden [15,35–37]. There is currently no literature with respect to TAA to guide decision-making on the optimal timing between exchanges, nor serologic cutoff values.

All patients, regardless of nonoperative or operative management, should be critically evaluated clinically and every effort to minimize the risk of wound breakdown should be pursued, including optimization of diabetes, reduction of inflammatory conditions, the absence of tobacco use and optimal nutrition. Soft tissue defects may require flap coverage. We recommend revision to ankle arthroplasty after clearance of infection.

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Authors: Eric Senneville, Gaston Slullitel, Valeria Lopez

QUESTION 8: What metrics can be used to determine the optimal timing of reimplantation in patients who have undergone resection arthroplasty as part of a two-stage exchange for infected total ankle arthroplasty (TAA)?

RECOMMENDATION: There is no conclusive data regarding what metrics can be used in order to determine the optimal timing of reimplantation for an infected TAA. We recommend that reimplantation is performed when there are clinical signs of resolution of infection (well-healed wound, lack of erythema, etc.), and the serological markers have substantially declined (> 40%) from baseline (measured at the time of diagnosis of infection).

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

Infected TAA is a serious complication that is thought to occur in as many as 5% of patients [1,2]. Management of infected TAA often requires surgical intervention that includes removal of the prosthesis, local and systemic antibiotic treatment, and subsequent reimplantation in a select group of patients. One of the most challenging questions pertains to optimal timing of reimplantation. There is little in the literature regarding the optimal treatment of an infected TAA. Most of the available literature has limitations including low numbers of patients, short duration of follow-up and so on [1–5].

There are a number of publications related to patients with infected TAA who underwent two-stage exchange arthroplasty. Patton et al. reported on 29 of 966 (3.2%) cases of infected TAA [3]. Among the infected TAA, 13 patients underwent two-stage exchange arthroplasty and antibiotic spacer placement. While infection type and operative cultures were listed, no specific recommendations on timing of reimplantation were made. Similarly, Lee et al. omitted data regarding timing of reimplantation but reported one case of deep infection, out of 50 TAAs (2%) that required implant removal, antibiotic-impregnated spacer placement, and later revision TAA [4].

Thoroughly outlining the timeline, Young et al. detailed a case report of a two-stage TAA revision [5]. Irrigation and debridement (cefazolin 1 gm diluted in 1L 0.9% saline) and antibiotic cement

spacer (80 gm of polymethylmethacrylate impregnated with 2 gm gentamicin) placement was implemented. The blood cultures and intraoperative bone and tissue cultures in the latter infected case isolated *Streptococcus mitis*. As a result, a six-week course of antibiotics with penicillin G was administered. Three months after infection had resolved, the patient had a revision TAA. As demonstrated, the limited TAA infection literature warrants that a treating orthopaedic surgeon applies the basic treatment principles derived from infections of knee and hip arthroplasties [6].

The ultimate decision regarding surgical management of patients with infected TAA in general, and reimplantation of those who have undergone a prior resection in particular, lies with the orthopaedic surgeon with appropriate consultation of other disciplines such as infectious disease specialists, plastic surgeons and so on. A two-stage exchange strategy is commonly indicated in patients who have a chronic infection and are not candidates for a one-stage exchange arthroplasty. Protocols for management of a patient with infected TAA are extrapolated from the available literature for infected hip and knee arthroplasties. Patients undergoing resection arthroplasty typically receive four to six weeks of intravenous or highly bioavailable oral antimicrobial therapy between stages [7,8].

The timing to reimplant usually relies on signs of clinical resolution of infection, such as healing of the wound, absence of erythema and so on, as well as a decline in serological markers of inflammation, namely erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) [9]. To determine infection resolution and predict the presence of infection in patients awaiting reimplantation, numerous serological markers have been evaluated in the past, including interleukin 6 (IL-6) and others [10]. The most widely used serological tests for the diagnosis of periprosthetic joint infection (PJI) are the assessment of ESR and CRP level. A recent publication also suggested the use of serum D-dimer combined with ESR and CRP in order to increase sensitivity and specificity [11].

In data published about hip and knee surgery, time from resection arthroplasty to reimplantation varies significantly from two weeks to several months. In earlier cohort studies, early reimplantation within three weeks after resection resulted in a higher failure rate [12,13]. Some groups have reported satisfactory outcomes when reimplantation occurs two to six weeks after resection while systemic antimicrobials are still being administered in situations when the infection is not due to MRSA, enterococci or any multidrug-resistant gram-negative organisms [14]. Delayed reimplantation after four to six weeks of intravenous antimicrobial therapy and an antibiotic-free period of two to eight weeks has been highly successful and chosen as the "standard" currently [7,15–17]. Recently, synovial fluid biomarkers have been shown to be useful in reaching or refuting the diagnosis of PJI. The combined measurement of synovial fluid alpha-defensin and CRP for the diagnosis of PJI demonstrated a sensitivity of 97% and a specificity of 100% [11,18]. Not only is obtaining synovial fluid invasive and painful to patients, but also there are not infrequent occasions when either an inadequate amount of fluid is available to perform all tests, or, worse, no fluid is retrieved from the joint [11].

Obtaining a pre-revision ESR and CRP is recommended to assess the success of treatment prior to reimplantation [19]. However, as some groups have reported, an elevated CRP level and ESR may not be accurate in predicting persistent infection post-resection, therefore the need for subsequent debridement should be interpreted in the context of the entire clinical picture when deciding on the appropriate timing for reimplantation [20–22].

In the absence of concrete data, and borrowing from the hip and knee infection literature, we recommend that reimplantation in patients with infected TAA be performed when appropriate antibiotic treatment is completed, clinical signs for resolution of infection are present (healed wound, absent erythema and so on) and the level of inflammatory markers of acute inflammation (ESR, CRP and possibly D-dimer) have declined substantially (> 40%) from their baseline. Further research regarding this issue is desperately is needed.

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Author: Elizabeth McDonald

QUESTION 9: What are the predictors of treatment failure in patients who have undergone two-stage exchange for infected total ankle arthroplasty (TAA)?

RECOMMENDATION: Predictors for treatment failure in patients undergoing two-stage exchange for infected TAA include compromised soft tissues (e.g., sinus tract, exposed hardware, etc.), significant bone involvement/osteomyelitis and insufficient timing of antibiotic course before reimplantation.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

The optimal management of patients with infected TAA is not well-known due to a limited number of studies [1–5]. While comparisons and deductions can be made from the knee and hip periprosthetic joint infection (PJI) literature on two-stage exchange, the management of infected TAA can differ from hip and knee arthroplasty because of the precarious soft tissue coverage around the ankle, the common history of multiple preceding operations in patients, and arthroplasty design updates coupled with limited surgical experience [3]. Two-stage exchange is a well-accepted surgical management approach for PJI.

There is limited detail in the TAA literature on two-stage exchange failure. A study by Patton et al. reported on 12 cases of two-stage revision for infected TAA but offered no details of the cases that failed [3]. Another study by Kessler et al. reported on 34 patients undergoing surgical management for infected TAA [6]. Of the patients treated for infected TAA, 10% (1/10) of two-stage exchanges resulted in failure. This two-stage failure is not described in detail. However, in the described cohort, the presence of compromised soft-tissue significantly increased the rate of failure after revision.

Another problem with the soft tissues surrounding the ankle is the presence of a sinus tract. Not only do sinus tracts often have indurated soft tissue around the ankle, but they also have the potential to limit preoperative cultures and organism identification, which in itself may predispose the patient to a future failure [7–11]. Furthermore, certain comorbidities such as metastatic disease, renal and/or liver dysfunction, and advanced cardiac disease are indicated to influence the rate of PJI [6,7], but these comorbidities may not necessarily be tied to treatment failure after two-stage exchange arthroplasty.

In North America patients undergoing two-stage exchange arthroplasty for the treatment of PJI are often subjected to six weeks of an antibiotic course. Based on data from hip and knee PJI, inadequate administration of antibiotics has been linked to the presence of positive cultures during reimplantation that, in turn, increase the risk of failure after reimplantation [8,13]. While inadequate antibiotic therapy has been linked with subsequent failure, the exact duration of antibiotic treatment, the benefit of intravenous (IV)-to-oral (PO) antibiotics, and the timing of IV-to-PO switch has not been determined. Recent PJI literature suggests that a short IV antibiotic period lasting at least five to seven days followed by pathogen-specific PO therapy may be a viable option for treatment of patients with PJI [14,15].

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QUESTION 10: How should postoperative cellulitis be treated in patients with total ankle arthroplasty (TAA) in place?

RECOMMENDATION: In the absence of evidence, we recommend that (1) patients with TAA in place who develop postoperative cellulitis be evaluated thoroughly to rule out periprosthetic joint infection of the ankle, and (2) that isolated cellulitis may be treated with antibiotics, elevation and close monitoring. Aspiration can be considered in certain cases, with the potential risk of introducing deep space infection.

LEVEL OF EVIDENCE: Consensus

DELEGATE VOTE: Agree: 92%, Disagree: 0%, Abstain: 8% (Super Majority, Strong Consensus)

RATIONALE

Treatment of postoperative cellulitis in patients with TAA is not well-defined. Schipper et al. suggested a compression wrap protocol over a circumferential fiberglass cast significantly reduces the incidence of wound complications [1]. While the authors demonstrated an overall reduction of wound complications, the differing postoperative immobilization protocols did not result in a significant difference in the proportion of wounds in patients with cellulitis requiring antibiotics (oral or intravenous) (22% vs. 16.7%, p = .60).

To our knowledge, there is no other TAA literature reporting on cellulitis. Brook and Frazier reported on 259 patients with culture-positive cellulitis [2]. Based upon their report in which 63 of 259 (24%) cellulitis cases were located on the leg, the authors concluded that the polymicrobial nature of cellulitis warrants the prescription of broad-spectrum antibiotics.

Meanwhile, in the total hip arthroplasty (THA) population, Rodriguez et al. reported on the use of intravenous and oral antibiotics in 16 patients with incisional cellulitis [3]. They assessed the erythematous eruption by hematological investigations, radiography, radionuclide scanning and blood culture, as well as aspiration from the area and skin biopsy. Following assessment, the best antibiotic course was determined. For two to six days until the erythema resolved, the following antibiotics were given to patients: 11 were given cephalexin, one vancomycin, one ampicillin and gentamicin and one cefuroxime. Following this antibiotic course, cephalexin, ciprofloxacin or amoxicillin were administered orally for two to six weeks. One patient received only oral ciprofloxacin, with resolution of the erythema occurring within 24 hours. Rodriquez et al. thus concluded that treatment with antibiotics for a minimum of two weeks led to resolution of symptoms and allowed for nonoperative management of the cellulitis.

In a separate case report on a patient undergoing THA, Perlick et al. argued that most cellulitis is caused by *Streptococcus hemolyticus* or *Staphylococcus aureus* [4]. The authors were successful in treating the surgical site cellulitis with the following protocol: dicloxacillin 2 gm × 3 or clindamycin 600 mg × 3 daily. This finding should also be considered when determining an appropriate treatment regimen for patients with post-arthroplasty cellulitis.

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Authors: Jonathan Kaplan, Steven Raikin

QUESTION 11: Does deep chronic infection after total ankle arthroplasty (TAA) require implant removal?

RECOMMENDATION: Yes. Deep chronic infection after TAA requires implant removal unless otherwise contraindicated.

LEVEL OF EVIDENCE: Strong

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

RATIONALE

While there is substantial evidence in the total hip arthroplasty (THA) and total knee arthroplasty (TKA) literature regarding one- and two-stage revision for infected total joint arthroplasty (TJA), there are very limited studies assessing deep chronic infection in primary TAA and TAA revisions. The majority of recommendations for the evaluation and treatment of the infected ankle arthroplasty in the current literature are based on those recommendations of THA or TKA [1–3]. Hsu et al. reported on the evaluation and management of the painful

TAA. In cases of deep infection in the early period (< 4 weeks), the authors recommended irrigation and drainage (I&D) with polyethylene exchange and intravenous (IV) antibiotics. In infection cases occurring > 4 weeks from the time of initial implantation, a two-stage surgery was required. However, it should be noted that this determination was again based on the THA and TKA literature rather than studies specifically assessing infected TAA [4].

Myerson et al. performed a retrospective review on the management of infection following total ankle replacement [5]. Over a 10-year period, the authors performed 613 total ankle replacements with a deep infection rate of 2.4%. There were 15 late/chronic infections, three early infections and one acute hematogenous infection. In the three early and one acute hematogenous infections, the authors attempted I&D, polyethylene exchange and retention of the components in conjunction with a course of IV antibiotics. Unfortunately, all four patients developed recurrent infection requiring repeat I&D and complete prosthesis removal with antibiotic spacer placement. In the chronic/late infections cohort, they performed a two-stage revision with initial I&D, complete explantation, cement spacer application and IV antibiotics. Of these 15 chronic infections, infection recurrence occurred in three patients, requiring additional interventions. Additionally, from the same institution, Ferrao et al. reported on the definitive treatment of infected total ankle replacements using an antibiotic cement spacer in cases in which revision would not be amenable [6].

In a related study, Patton et al. reported on their experience with infected TAA [3]. Out of 966 patients undergoing TAA, there were a total of 29 infections, accounting for an overall infection rate of 3.2%. They classified these based on acute postoperative complications including cellulitis or wound dehiscence, late chronic infection or remote hematogenous. There were 11 cases of acute postoperative wound dehiscence, three cases of acute postoperative cellulitis, eight cases of remote hematogenous infection and seven cases of late chronic infection. Of the 14 cases in the acute stage (cellulitis and wound dehiscence), one was treated with I&D, polyethylene exchange and antibiotic treatment, three were treated with I&D and antibiotics, four were treated with two-stage exchange revision, one was treated with a one-stage revision, one was treated with permanent antibiotic spacer placement and four were treated with amputation. Of the seven late chronic infections, five were treated with two-stage procedures, one was treated with amputation and one was treated with polyethylene exchange. In the eight cases of remote hematogenous infection, one was treated with amputation, six were treated with two-stage procedures and one was treated with I&D. While the authors report a variety of procedures for each of these presentations based on timing, it should be noted that they defined infection in the early postoperative phase as cellulitis and wound dehiscence rather than an objective diagnosis of deep infection. Additionally, while there were cases of single-stage procedures, these were quite low numbers compared to two-stage procedures or even amputation.

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3.2. TREATMENT: NON-TOTAL ANKLE ARTHROPLASTY-SPECIFIC

Authors: Kent Ellington, Christopher Hirose, Thomas B. Bemenderfer

QUESTION 1: What is the treatment "algorithm" for infection after ankle or hindfoot arthrodesis?

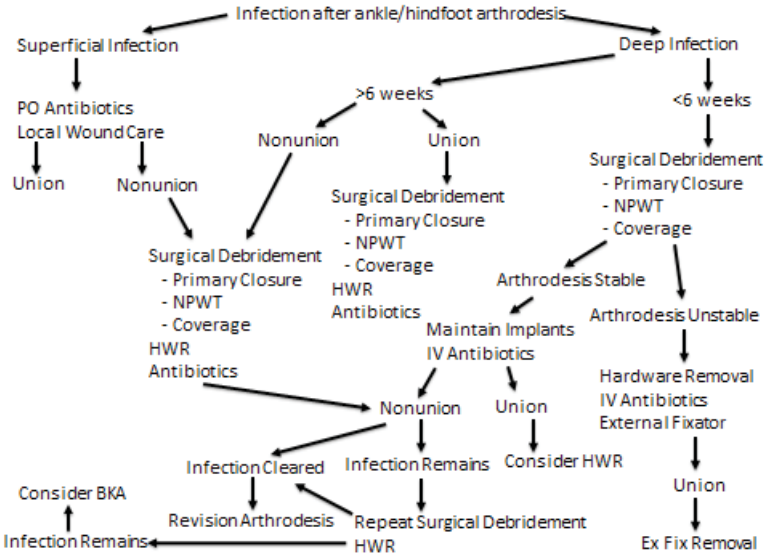
RECOMMENDATION: There is no universal algorithm for addressing the infected ankle or subtalar arthrodesis. A potential algorithm created by consensus is:

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

Infection after ankle or hindfoot arthrodesis always results in a protracted recovery. Recovery from this complication may include multiple surgeries, escalating cost and may result in a painful and poorly-functioning limb. Patients with suspicion of infection following ankle or hindfoot arthrodesis should be evaluated for deep versus superficial infection as well as appropriate host and surgical factors to determine the most appropriate treatment. Superficial infections may be treated with irrigation and debridement (I&D), local wound care and pathogen-specific antibiotics. Deep infections involving the internal hardware should prompt hardware removal. Additional components of treatment may include some combination of placement of antibiotic beads or spacers, stabilization with external fixation to temporarily stabilize or achieve definitive arthrodesis [1] and delayed revision arthrodesis with internal fixa-



HWR, hardware removal; NPWT, negative-pressure wound therapy

tion following eradication of infection. The patient's nutritional and vascular status should be optimized. If soft tissue coverage is necessary, a multidisciplinary approach is necessary to determine the viability of the extremity. To achieve fusion, a radical debridement, stable fixation and minimal compromise of the marginal blood supply are necessary.

All patients should be critically evaluated in a multidisciplinary approach to optimize the patient's health and psychological status. Every effort to minimize the risk of wound breakdown should be pursued including optimization of diabetes, reduction of inflammatory conditions, the absence of tobacco use and optimal nutrition. The impact of prolonged impaired mobilization, possible unemployment and social isolation should not be neglected and may compromise patient adherence for further surgery and postoperative regimens, as well as diminish functional outcomes. We recommend an appropriate evaluation of the patient host and arthrodesis surgical factors in patients with infection following tibiotalar or subtalar arthrodesis.

Infection following ankle or hindfoot arthrodesis may significantly delay bony consolidation. Frey et al. reported as high as 60% nonunion rate following ankle fusion complicated by infection [2]. In order to address the infected ankle or hindfoot fusion, several algorithms have been proposed [1,3]. Any patient in which bony fusion is uncertain should be evaluated by computerized tomography (CT) to assess the arthrodesis. Debridement followed by arthrodesis remains the salvage procedure of choice for the infected ankle and subtalar joints, and has proven to be an effective means for limb salvage and maximizing patient functional outcome [1,3–5]. Härle reported the results of a two-stage procedure with the treatment of infection first by implant removal, thorough debridement and implantation of Septopal® (Gentamicin-PMMA chains) beads, followed by secondary internal stabilization with an antibiotic-releasing bone plate. Although 3 of the 42 patients (7%) ultimately required an amputation, infection was cured long-term in 36 (84%), and 39 (93%) achieved stable bony fusion [3]. Paley et al. recommended removal of all internal hardware and sharp debridement of all necrotic and infected tissue followed by external fixation and reported 100% union [1]. Baumhauer et al. reviewed the literature on arthrodesis of an infected ankle and subtalar joint but did not suggest an algorithm for treatment of infection after ankle or subtalar joint, arthrodesis [6].

Host Factors

Host factors must be optimized prior to undergoing reoperation. Malnutrition, diabetes and nicotine cessation should be advocated. Preoperative malnutrition has been associated with delayed wound healing [7], longer length of stay and anesthesia/surgical times [8] and failure of treatment of persistently draining wounds inevitably leading to deep infection [9]. The measures of malnutrition have varied and may be defined by a variety of methods including serological laboratory values (e.g., transferrin, total lymphocyte count, serum albumin and prealbumin), anthropometric measurements, and standardized scoring tools [10]. The most common definitions of malnutrition are total lymphocyte count (TLC < 1500/cc) and serum albumin (< 3.5 gm/dL) [9,11,12]. Frey et al. reported that patients with major medical problems including renal failure, significant smoking history, diabetes and alcohol abuse demonstrate an 85% nonunion rate following attempted ankle fusion [2]. Jaberi et al. reported successful salvage of patients undergoing hip and knee arthroplasty in only 5% of malnourished patients treated with I&D [9].

Diabetes

Perioperatively elevated blood glucose levels and complicated diabetes mellitus prior to elective surgery predispose patients to postoperative soft tissue and bone healing complications [13–18]. The current guidelines, as published by the American Diabetes Association, recommend that surgery should be avoided if possible for those patients with hemoglobin A1c (HbA1c) greater than 7% [19]. In an effort to validate the recommendation, Jupiter et al. assessed the relationship between the HbA1c levels and the rate of postoperative infection [20]. Their results indicated that infection rates increase steadily as the HbA1c increases toward 7.3%, increase rapidly at an HbA1c of 7.3% to 9.8%, and then level off. Several studies demonstrate an increased risk of infection following arthroplasty in patients

with HbA1c greater than 6.5% [20–22]. Although it is unclear in foot and ankle literature whether any specific HbA1c should serve as a contraindication for revision fusion, multiple studies have demonstrated that diabetic neuropathic arthropathy contributes to high complication and failure rates. Ankle and subtalar arthrodesis should thus be considered with caution in the diabetic patient [23].

Tobacco

All efforts should be made to eliminate exposure to nicotine and tobacco products. Studies have demonstrated that patients who smoke tobacco are at three times greater risk of hindfoot nonunion [24]. Fragomen et al. reported a 54% nonunion rate in tobacco users who smoke undergoing primary arthrodesis [25]. Patients who undergo revision are certainly at higher risk of both osseous nonunion and soft tissue complications following revision hindfoot nonunion. Although the literature is unclear, we recommend waiting at least six weeks following smoking cessation in order to reduce the risk of pulmonary complications associated with rebound mucosal secretions and increased perioperative complications associated with smoking cessation in the perioperative period. In addition, we recommend confirming cessation via testing for nicotine and its primary breakdown product (metabolite) cotinine in the blood, urine, saliva or hair. Cotinine is widely used when compared to other diagnostic tools because of its higher sensitivity, specificity and long half-life, as well as the fact that it is the best indicator for distinguishing the tobacco users from non-users. We prefer urine biomarker testing over serum given its high sensitivity compared to blood cotinine and minimally invasive collection [26,27]. We recommend a urinary cutoff of greater than or equal to 2.47 ng/ml to detect the highest sensitivity and specificity of 100% for smoking [28].

SURGICAL PROCEDURES

Irrigation and Debridement

Isolated surgical I&D should be reserved for soft tissue infections that are not in direct communication with hardware. Given the risk of persistent chronic infection following infected ankle or hindfoot arthrodesis, we do not recommend isolated I&D of the deeply infected arthrodesis. If there is any uncertainty concerning whether the retained hardware is in communication with infected tissue, the hardware should be removed given the high failure rate associated with retained hardware [1,3–5].

Soft Tissue Coverage

The overlying soft tissue must be evaluated to determine whether adequate soft tissue coverage is possible; sinus tracts may be excised and hardware remains exposed. Multidisciplinary assistance from plastic surgery may be necessary if primary or delayed primary is not possible and if the surgical site necessitates a local or free flap for closure. Commonly utilized flaps for the hindfoot may include reverse sural flap or free flap (e.g., anterolateral thigh via the circumflex femoral pedicle, superficial circumflex iliac artery perforator and thoracodorsal artery perforator flaps) [29].

Bone Stock

Viable bone must be evaluated to determine remaining available bone for reconstruction and possible salvage arthrodesis [30]. There are limited case reports of salvage tibiotalocalcaneal (TTC) arthrodesis with a custom titanium alloy truss and retrograde intramedullary nail for hindfoot infection with bone loss [31]. We were unable to identify any clear literature on the most appropriate management of the infected ankle and subtalar arthrodesis with significant osteolysis, subsidence or bone loss following excision of bone with osteomyelitis.

Explantation of Hardware

In 1999, Costerton attributed the persistence of certain chronic infections to the presence of biofilm, and since then the majority of implant-related infections in orthopaedics are believed to be biofilm-related infections associated with glycocalyx polysaccharide biofilms that are often recalcitrant to antibiotic treatment and may be culture-negative with ineffective clearance from the host [32,33]. Given the risk of biofilm-related infections, reimplantation of a prosthesis should be delayed until adequate resuscitation and eradication of the offending organism has been completed [34–44]. However, Paley et al. supported using external fixation following explantation of hardware in the infected failed hindfoot fusion [1].

FIXATION TECHNIQUES

Internal Osteosynthesis

Several techniques have been reported for utilizing plate fixation for revision ankle arthrodeses [45–49]. However, successful internal fixation following infection has only been described in the setting of the septic ankle. Klouche et al. reported the outcomes of 20 patients who underwent tibiotalar arthrodesis in the presence of sepsis with internal osteosynthesis resulting in a fusion rate of 89.5% and clearance in 85.0% of cases [50]. Richter et al. reported solid ankle or hindfoot arthrodesis following infection in 39 of 45 patients (87%) utilizing hybrid fixation with both internal (compression screws and an anterior plate) and external fixation [51].

External Fixator

TTC arthrodesis using the Ilizarov technique is a viable alternative to amputation in patients with infected nonunions or large bone loss of the tibia or talus precluding internal fixation with reported fusion rates as high as 77 to 93% [5,52–54]. Saltzman reported on eight patients with diffuse ankle osteomyelitis who were treated with resection of the infected bone and application of a compressive circular external fixator. Six weeks of intravenous antibiotics were administered and wound vacuum devices were applied over open wounds. Sepsis was eradicated in all [55]. It should be noted that these patients had the diagnosis of osteomyelitis, but not specifically an infected ankle or hindfoot arthrodesis. Similarly, Raikin recommended I&D, a six-week course of intravenous antibiotics, removal of internal hardware and stabilization of the arthrodesis with an external fixator. A vacuum device or plastic surgery coverage was recommended for an open wound [56]. For failed ankle arthrodeses, Hawkins et al. reported on 21 cases which were salvaged with the Ilizarov technique. Of the patients 80% achieved fusion and resolved infection [57]. Although external fixation is typically indicated for patients with active or previous infection, union rates and outcome measures of external fixation are inferior to internal fixation [58].

Intramedullary Fixation

Techniques utilizing an antibiotic-impregnated intramedullary polymethyl methacrylate (PMMA) nail or antibiotic-coated intramedullary nail have been described [59–61]. To achieve successful fusion in the setting of infection, it is important to not only remove any hardware with potential formation of glycocalyx polysaccharide biofilm but also to avoid introducing new foreign bodies at the site of infection, and, therefore, external fixation is often

considered the gold standard. However, antibiotic-coated intramedullary nails may also be considered if acute shortening and bone contact may be achieved [61,62]. The current literature supporting antibiotic-coated nails for the treatment of infected ankle nonunions and infected distal tibial fractures to achieve fusion, improve patient functional outcomes and successfully eradicate infection are encouraging. However, these studies are limited to small case series. Future studies are necessary to better understand the potential for union, functional outcome and infection control utilizing intramedullary antibiotic-coated nails following infected ankle or hindfoot arthrodesis.

USE OF ANTIBIOTIC-IMPREGNATED ADJUNCT

All patients with infection following ankle or hindfoot arthrodesis procedures should be administered oral, intravenous and/or local antibiotics. Consulting your local infectious disease physician may be warranted to better assess local antibiotic nomograms and assist in recommendations. Antibiotic-loaded PMMA has demonstrated to be successful in treating osteomyelitis and is commonly used for antibiotic release to the site of infection but displays variable elution kinetics and represents a potential nidus for infection, therefore requiring surgical removal once antibiotics have eluted [63,64]. Definitive treatment with an antibiotic spacer can be considered and has been reported. Ferrao et al. reported on the use of a cement spacer after deep ankle infection. Three patients underwent an ankle arthrodesis, and the remaining six underwent TAA. Most retained their cement spacers, and those who did were ambulatory with little discomfort [65]. Alternatively, antibiotic-loaded calcium sulfate beads have the benefit of serving as an osteoconductive material with time-dependent antibiotic delivery, but have been criticized for the massive amount of drainage secondary to hydrolysis-dependent antibiotic delivery [66]. The concept of local antibiotic deposition is particularly critical in poorly-perfused limbs. The use of antibiotics in bone cement or calcium sulfate biocomposites offers several advantages, including the ability to achieve high local levels of antibiotic [67], low systemic toxicity [68,69] and minimal local tissue toxicity [70,71]. The high local antibiotic levels achieved also allows for a decreased need for systemic antibiotic usage, which is especially useful in patients who are intolerant to prolonged systemic antibiotics [64].

Amputation

Surgeons making a choice between arthrodesis and amputation need to consider the clinical situation of the individual and patient preference. Amputation of the failed infected hindfoot arthrodesis may be appropriate in select cases involving non-ambulatory patients, infection resistant to aggressive debridement and antibiotics, severe bone loss or extensive osteomyelitis that precludes arthrodesis, inadequate soft tissue coverage or peripheral vascular or neurovascular injury. Severe immunocompromising states inhibit both infection eradication and wound healing and may be prohibitive for revision or may necessitate amputation. Active intravenous drug abuse may be a contraindication to salvage of the failed infected hindfoot fusion and may also indicate the need for an amputation. Contraindications to revision may apply to non-ambulatory patients or those with extensive medical comorbidity that precludes multiple surgeries.

Biophysical Augmentation

Biological supplementation has been studied in at-risk ankle unions as well as nonunions. Given the reported high rates of nonunion and malunion in primary hindfoot and ankle unions [72], it is common practice to use some biological adjunct therapy to improve the chance of fusion including bone marrow aspirate, platelet-rich plasma (PRP), recombinant human bone morphogenetic protein-2 (rhBMP-2), cancellous bone allograft, recombinant human platelet-derived growth factor (rhPDGF-BB) in combination with a ß-TCP-collagen matrix, cryopreserved cellular bone allograft, map3 cellular allogeneic bone graft and cryopreserved amniotic membrane-umbilical cord allograft [73–77]. No study has specifically evaluated the efficacy and safety of biological adjuncts in the setting of the infected ankle and hindfoot nonunion.

Various external and internal osteobiologic devices have been shown to promote healing when used in complex ankle fusion. Three commercially distinct modalities have been investigated for bone stimulation, including pulsed electromagnetic field [77,78], internal direct current [79–82] and low-intensity pulsed ultrasound [83–85]. However, no study has specifically evaluated the impact of biophysical adjuncts following infected ankle or subtalar arthrodesis and further additional randomized controlled trials are necessary before justifying their utility.

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QUESTION 2: What is the optimal antibiotic (type, dose and route of administration) treatment for infections after foot/ankle fracture or fusion procedures?

RECOMMENDATION: The optimal antibiotic treatment after foot/ankle fractures or fusion should be determined based on the result of culture. In the absence of culture results, administered antibiotics should include coverage against common pathogens such as *Staphylococcus aureus*.

LEVEL OF EVIDENCE: Strong

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

RATIONALE

The commonality in the literature when addressing infection following traumatic foot/ankle procedures or fusions is to target antibiotic therapy to the specific pathogen [1–6]. This is achieved by taking intraoperative cultures, often preceded by preoperative joint aspiration. The majority of the literature suggests a six-week course of intravenous antibiotics; however, the range of recommended therapy is five days to three months [2,5,7].

The second method for delivery of antibiotics is by the incorporation of the antimicrobial agents into the cement spacer when surgical intervention is used [1,2,8]. Since conventional cultures used to identify the infecting organism are often obtained at the time of surgery, the offending pathogen is often not known preoperatively. In this situation, or when the culture results are negative, broad-spectrum antibiotics should be administered. Vancomycin is most commonly used, not infrequently in conjunction with tobramycin or gentamycin [1,5,9].

Methicillin-sensitive *Staphylococcus aureus* (MSSA) is the most common pathogen identified with post-traumatic/post-fusion foot and ankle infections [1,4,6,10,11]. The second most common infectious organism is *Staphylococcus epidermidis* [6,12]. Multi-drug resistant organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA), are also isolated in cultures with some regularity [6,11]. Diabetic patients have some increased risk of *Pseudomonas* infections as compared to non-diabetics [4]. Importantly, rare bacteria have been identified in case reports and polymicrobial infections have been regularly reported as well [5,13].

There is great heterogeneity in those patients being treated for post-traumatic/post-fusion infection, so it is difficult to interpret outcomes with regard to recurrent infection, ambulatory status/functionality and bony union [1,2]. Stability contributes to the resolution of infection and it has been proposed that antibiotic-coated retrograde nails can also provide local antibiotic delivery [14]. Even for those patients deemed inappropriate for a return to the operating room and for those treated definitively with an antibiotic-laden spacer, independent ambulation can be reliably achieved [3].

In conclusion, we recommend that the treatment of any foot and ankle infections following fracture or fusion procedures be based on the results of the culture, whenever available. In the absence of culture results, broad-spectrum antibiotics should be used.

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QUESTION 3: What is the treatment "algorithm" for infection after Achilles tendon repair/reconstruction?

RECOMMENDATION: The initial treatment of an infected Achilles tendon reconstruction should include thorough debridement of all infected tissues with the removal of retained sutures or foreign material. Cultures should be taken at the time of debridement and antibiotic administration should be dictated by the result of culture and continued until inflammatory markers and clinical symptoms normalize. If significant soft tissue defect in the overlying area remains, the choice of tendon reconstruction and/or transfer with soft tissue coverage should be left up to the discretion of the treating surgeon based on preference and expertise. Revision reconstruction should be delayed until the infection is cleared.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Infection following Achilles tendon repair/reconstruction is a potentially catastrophic complication of a relatively common orthopaedic procedure. Wound complications following Achilles tendon repair occur in approximately 10% of cases [1], although the proportion of patients requiring secondary surgery or prolonged care has been reported to be substantially lower (2.44%) [2]. The loss of Achilles tendon tissue and soft tissue coverage secondary to infection leads to poor results and can be difficult to manage [3].

The optimal treatment of an infection following Achilles tendon repair/reconstruction consists of infection eradication, maintenance or restoration of ankle plantar flexion and soft tissue coverage. A literature search for the treatment of infection following Achilles tendon repair/reconstruction reveals a heterogeneous collection of expert opinions and case reports/series on how to accomplish these goals, with no definite consensus. While the literature generally agrees that the most important aspect of treatment revolves around an extensive debridement of the infected/necrotic tissue and antibiotic coverage, each author has their own opinion on how tendon and soft tissue defects should be addressed. These opinions range from extensive debridement with functional rehabilitation alone [4,5], to local tendon/tissue transfer [6–11], to free flaps [12–17]. Additional variations of treatment include single versus staged procedures [18,19], the utilization of cement spacers [18,19], tissue expanders [19] and negative pressure wound therapy [20,21].

Given the heterogeneity of the literature and the lack of any high level of evidence publications on the subject matter, we are unable to formulate a definitive consensus statement with regards to soft tissue coverage of the infected Achilles tendon following a prior repair/reconstruction. There is, however, evidence to suggest that thorough debridement of all infected tissue with the removal of retained suture or foreign material and antibiotic administration should be the initial step in the treatment of these patients. Cultures should also be taken at the time of debridement and antibiotic administration should be culture-driven and continued until inflammatory markers and clinical symptoms normalize. If significant defects remain in the Achilles tendon and overlying soft tissue following debridement, the choice of tendon reconstruction and/or transfer with soft tissue coverage should be left to the discretion of the treating surgeon based on preference and expertise.

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QUESTION 4: Should treatment of diabetic foot osteomyelitis be based on bone biopsies?

RECOMMENDATION: Yes. Bone biopsies play both a crucial diagnostic and interventional role in the management of diabetic foot infection. While bone biopsies are not required in every case of diabetic foot infection, their most important role is in guiding accurate antibiotic treatment, as they provide more accurate microbiological information than superficial soft tissue samples in patients with diabetic foot osteomyelitis.

LEVEL OF EVIDENCE: Moderate

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

RATIONALE

Diabetic foot infections of the skin and soft tissue can lead to contiguous spread to underlying bone, resulting in osteomyelitis. Where a diabetic foot ulcer fails to heal with no other apparent reason or when exposure of bone is observed, osteomyelitis should be suspected. Plain radiography has demonstrated to have poor sensitivity in detecting osteomyelitis in the early stages [1].

Moreover, plain radiography and other imaging modalities do not identify pathogenic organisms, and, thus cannot guide antibiotic therapy. Despite the ease of obtaining superficial wound swab cultures, the cultured organisms are polymicrobial and do not correlate well with bone biopsy cultures and, therefore, should not be used to guide antibiotic therapies [2–6]. A single retrospective multicenter cohort study reported that the rate of infection resolution was significantly higher in the group for whom the choice of antibiotic regimen was based on bone culture versus those based on wound swab culture (82% vs. 50%, p = 0.02) [7].

Bone biopsies taken for microbiological and histopathological analysis are the gold standard for a definitive diagnosis of osteomyelitis [8–10]. A specimen can be obtained either transcutaneously through uninfected skin or as part of an operative procedure following debridement. Bone biopsies play both a crucial diagnostic as well as interventional role in the management of diabetic foot infection. While bone biopsies are not required in every case of diabetic foot infection, their most important role is in guiding accurate antibiotic treatment.

A positive microbiological result is where one or more pathogens from a reliably-obtained bone specimen is cultured [11]. It has shown to give a sensitivity of 92% and specificity of 60% in diagnosing diabetic foot osteomyelitis [12]. Reliable and accurate identification of the causative pathogens in diabetic foot infections is important, as prolonged antimicrobial therapy is tailored according to microbiological susceptibility profile. Most diabetic foot osteomyelitis cases are polymicrobial, with *Staphylococcus aureus* being the most commonly isolated pathogen (50% of cases). Other frequently isolated organisms include coagulase-negative staphylococci, *Enterobacteriaceae*, aerobic streptococci and *Pseudomonas aeruginosa* [8,13,14]. Contamination of contiguous wound colonizing flora and skin commensals may give a false positive result, whereas prior antibiotic therapy, patchy infectious involvement or inability to culture fastidious organisms may yield false-negative results [11].

Positive histological findings include aggregates of inflammatory cells (neutrophils, lymphocytes, histiocytes and plasma cells), erosion of trabecular bone, marrow changes (fat necrosis, edema, fibrosis and reactive bone formation) [11,15,16]. Other causes of inflammation may give false-positive histological results, whereas sampling errors can give a false-negative result. Histological analysis may have better sensitivity than bacteriological cultures, as the latter is often performed under flawed conditions. However, a study by Meyr et al. has questioned the statistical reliability of the histopathologic diagnosis of diabetic foot osteomyelitis using bone biopsies, quoting a 41% of clinically significant disagreement between different pathologists, falling short of what would be expected of a “reference standard” [16]. This highlights the controversy in histopathological patterns and findings that pathologists use as a reference to establish a diagnosis of osteomyelitis [15,17,18].

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