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

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

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

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3.2. TREATMENT: NON-TOTAL ANKLE ARTHROPLASTY-SPECIFIC

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

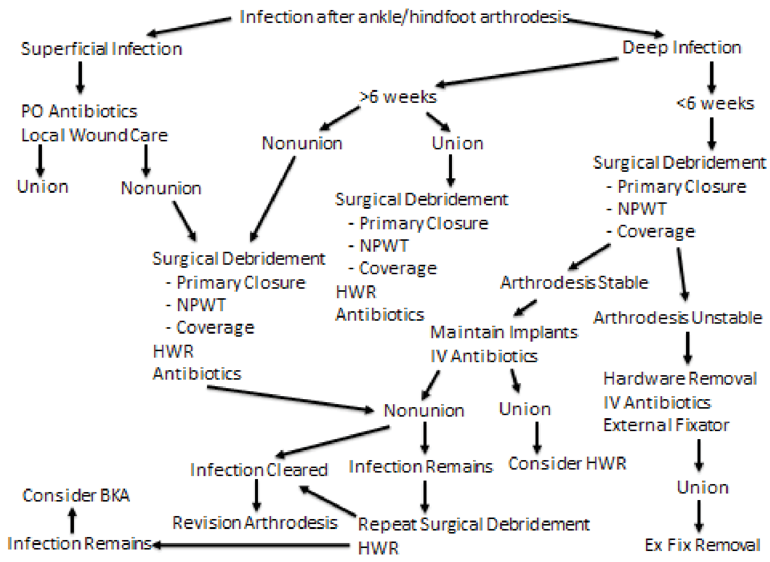
RECOMMENDATION: There is no universal algorithm for addressing the infected ankle or subtalar arthrodesis. A potential algorithm created by consensus is:

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

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



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

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

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

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

Host Factors

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

Diabetes

Perioperatively elevated blood glucose levels and complicated diabetes mellitus prior to elective surgery predispose patients to postoperative soft tissue and bone healing complications [13–18]. The current guidelines, as published by the American Diabetes Association, recommend that surgery should be avoided if possible for those patients with hemoglobin A1c (HbA1c) greater than 7% [19]. In an effort to validate the recommendation, Jupiter et al. assessed the relationship between the HbA1c levels and the rate of postoperative infection [20]. Their results indicated that infection rates increase steadily as the HbA1c increases toward 7.3%, increase rapidly at an HbA1c of 7.3% to 9.8%, and then level off. Several studies demonstrate an increased risk of infection following arthroplasty in patients with HbA1c greater than 6.5% [20–22]. Although it is unclear in foot and ankle literature whether any specific HbA1c should serve as a contraindication for revision fusion, multiple studies have demonstrated that diabetic neuropathic arthropathy contributes to high complication and failure rates. Ankle and subtalar arthrodesis should thus be considered with caution in the diabetic patient [23].

Tobacco

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

SURGICAL PROCEDURES

Irrigation and Debridement

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

Soft Tissue Coverage

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

Bone Stock

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

Explantation of Hardware

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

FIXATION TECHNIQUES

Internal Osteosynthesis

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

External Fixator

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

Intramedullary Fixation

Techniques utilizing an antibiotic-impregnated intramedullary polymethyl methacrylate (PMMA) nail or antibiotic-coated intramedullary nail have been described [59–61]. To achieve successful fusion in the setting of infection, it is important to not only remove any hardware with potential formation of glycocalyx polysaccharide biofilm but also to avoid introducing new foreign bodies at the site of infection, and, therefore, external fixation is often considered the gold standard. However, antibiotic-coated intramedullary nails may also be considered if acute shortening and bone contact may be achieved [61,62]. The current literature supporting antibiotic-coated nails for the treatment of infected ankle nonunions and infected distal tibial fractures to achieve fusion, improve patient functional outcomes and successfully eradicate infection are encouraging. However, these studies are limited to small case series. Future studies are necessary to better understand the potential for union, functional outcome and infection control utilizing intramedullary antibiotic-coated nails following infected ankle or hindfoot arthrodesis.

USE OF ANTIBIOTIC-IMPREGNATED ADJUNCT

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

Amputation

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

Biophysical Augmentation

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

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

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

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

LEVEL OF EVIDENCE: Strong

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

RATIONALE

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

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

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

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

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

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