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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