One study suggested that the custom-made cement spacer that contains specific antibiotics targeted towards the infective organism(s) should be made after consultation with a microbiologist or infectious disease specialist [6]. Antibiotics like gentamicin, vancomycin, ampicillin, clindamycin and meropenem can be used as a combination based on organism susceptibility [4,6,14]. Even in cases of multi-resistant germs like methicillin-resistant *Staphylococcus aureus*/methicillin-resistant *Staphylococcus epidermidis* (MRSA/MRSE), it was possible to achieve a 100% infection control rate when the local antibiotic therapy was tailored towards the infecting organism(s) [11]. It is, however, a known fact that antibiotic elution from spacers decreases over time. Studies have shown that bacterial colonization of spacers can occur with increasing in situ time [18,20–22]. Antibiotic cement spacers, thus, play a role for a finite period of time and should be removed at some point.

Another question that remains is whether antibiotics should be added to cement, if used, during reimplantation surgery and, if added, whether the antibiotics should be tailored towards the infective agent. This question has been answered comprehensively elsewhere in the consensus document, citing all the supportive literature. It is, however, our opinion that the addition of targeted antibiotics to cement, if used during reimplantation, may also play a role in reducing the incidence of subsequent failure.

In conclusion, based on a review of the available evidence, it is recommended that the type of antibiotics added to the cement spacer should be targeted towards the infective organism(s) and their susceptibility as determined by preoperative culture. In cases of culture-negative PJIs, strong consideration should be given for the addition of broad-spectrum antibiotics to cement spacers that have activity against the most common organisms causing PJIs.

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QUESTION 4: Which antibiotic(s) should be added to a cement spacer in patients with periprosthetic joint infections (PJIs) caused by multiresistant organisms?

RECOMMENDATION: In the case of PJIs caused by methicillin-resistant *Staphylococcus* aureus/methicillin-resistant *Staphylococcus epidermidis* (MRSA/MRSE), vancomycin should be added to the bone cement spacer. In vancomycin-resistant strains, such as vancomycin-resistant Enterococcus (VRE), or in multiresistant gram-negative PJI cases, individual decision making is mandatory based on the known susceptibilities. Consultation with a microbiologist/infectious disease specialist is strongly recommended.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 99%, Disagree: 0%, Abstain: 1% (Unanimous, Strongest Consensus)

RATIONALE

Multidrug resistant (MDR) pathogens in the context of periprosthetic joint infections (PJIs) are MRSA, MRSE or VRE and multidrug-resistant gram-negatives (MRGN).

Most PJIs are caused by gram-positive cocci, including *Staphylococcus* species [1], and in some reports methicillin-resistant organisms account for up to 74% of PJIs [2]. For the treatment of PJIs caused by MRSA, vancomycin is usually used for antibiotic therapy and commonly incorporated into bone cement as well as intravenous treatment [3]. The successful clinical control of chronic PJIs due to methicillin-resistant organisms varies from 48 - 89% [4,5] in the hip and 60 - 74% [6,7] in the knee when vancomycin is used in two-stage exchange arthroplasty.

The optimal combination of antibiotics in polymethyl methacrylate cement is not known. Most surgeons prefer to add between two to four grams of vancomycin and a similar dose of an aminoglycoside, such as gentamicin or tobramycin, to the cement. The addition of dual antibiotics to cement has several advantages including a postulated synergy between vancomycin and gentamicin against gram-positive bacteria [8,9] and an improved antibiotic elution from the spacer [10,11]. Moreover, this antibiotic combination results in a decreased risk of bacterial growth on the surface of the cement spacer, which could be detrimental to thecontrol of the infection [10]. Systemic toxicity as a result of elution of antibiotics from cement spacers, though rare, can occur. Thus, it is important to ensure that the renal clearance of the patient and the viscosity of the cement, which affects antibiotic elution, is considered when forming the spacer during resection arthroplasty. Renal toxicity of vancomycin is a potential risk and renal function should be monitored [11,12]. However, Hsieh et al. noted no systemic adverse effects after using high doses of vancomycin and aztreonam in bone cement in 46 patients with a PJI of the hip [13]. Also, Springer et al. reported no systemic adverse effects from the use of high doses of vancomycin and gentamicin in cement spacers in a series of 36 knees with PJIs [14].

Regarding susceptible gram-negative bacteria, third-generation cephalosporins [15], carbapenems [16–19] and monobactam antibiotics [13] have strong activity. They retain their antibacterial capacities after being added into bone cement, but they exhibit different antibacterial durations even when the same antibiotic dose has been used. The kinetics of antibiotic release from bone cement depends on the penetration of dissolution fluids into the polymer matrix and subsequent diffusion of the dissolved drug from the cement [20]. Consequently, the limiting factor that determines the antibacterial activity of the cement is the efficiency of antibiotic elution.

The published literature on the topic of what antibiotics should be added to cement spacers for management of PJIs caused by resistant organisms is not well-established. A few reports exist related to management of PJIs caused by MRSA and MRSE with less literature related to the management of PJIs caused by multi-resistant gram-negative organisms. Numerous factors need to be considered when adding antibiotics to cement, including the renal function of the host, the antibiogram of the organism, the type of cement being used, the allergy profile of the host and so forth. In addition, other patient comorbidities, duration and type of intravenous/oral (IV/PO) antibiotics after spacer placement and the quality of bone and soft tissues should be taken into consideration.

The objective of adding antibiotics to cement spacers is to allow for high elution of antibiotics into the affected joint that will reach beyond the organism minimum inhibitory concentration while avoiding potential for systemic drug toxicity [14,21]. It is important to note that on occasion alternative antibiotics may be added to cement spacers based on the allergy profile of the patient.

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