of these hips achieved a sensitivity of only 13% and a specificity of 98%. They concluded that aspiration is of limited diagnostic validity and cannot reliably detect or rule out infection. However, they highlighted the fact that a positive aspiration culture had a high diagnostic performance.

Recently, serum D-dimer tests have been proposed as promising tests for diagnosing PJIs [7]. The study evaluated the role of D-dimer in detecting the presence of infection at the time of reimplantation. Out of five patients with raised D-dimer levels at the time of reimplantation, two had a positive culture from samples taken during reimplantation and subsequently failed. It is worth mentioning that both ESR and CRP values were normal in these two patients.

As previously mentioned, there is no gold standard test for PJIs. After spacer insertion and a period of antibiotic treatment, infection control is expected and laboratory and clinical signs are expected to improve.

In the setting of a failure to improve or if there is ongoing active infection at the time of planned reimplantation, a repeated irrigation, debridement and spacer exchange may be considered. Further research is essential to establish effective tests that prove eradication of PJIs and therefore determine if reimplantation should be performed. The role of several tests, such as elevated ESR and CRP, synovial WBC, and PMN % as well as serum D-dimer are helpful in determining whether reimplantation can be carried out but are not absolute determinants. A combination of these tests, clinical suspicion, completion of antibiotic therapy and careful evaluation of MusculoSkeletal Infection Society (MSIS) criteria [17] should be used to determine if a repeated cement spacer exchange may be indicated. Repeated I&D of an implanted spacer, without antibiotic spacer exchange, does not seem to have any evidence and is generally considered a suboptimal approach in this setting.

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Authors: Akos Zahar, Andrew Porteous, Viktor Janz, Ankit Varshneya, Vishwas Sharma

QUESTION 3: Should the antibiotics placed in a cement spacer be tailored to the sensitivity of the infective organism?

RECOMMENDATION: Antibiotics added to cement spacer during resection arthroplasty should be tailored towards the causative organism and its susceptibility. In case of culture negative periprosthetic joint infections (PJIs), consideration should be given to the addition of a broad-spectrum antibiotic to the cement spacer to cover the most potential pathogens causing PJI.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 94%, Disagree: 3%, Abstain: 3% (Super Majority, Strong Consensus)

RATIONALE

The literature was reviewed to identify all publications related to the above question. The systemic review revealed 12 publications with clear information about tailored local antibiotics in bone cement spacers. The majority of the papers were retrospective studies with a relatively low number of patients in each report. One study by Hsieh et al. contained 99 patients, which was the largest cohort [1]. There were two review articles from the same group [2,3]. Kiniet al. reviewed the available literature that consisted of 17 publications related to hip infections and 18 studies related to PJIs of the knee. They did not find clear evidence related to the issue of antibiotics

added to cement, but believed that the literature is supportive of the concept that the antibiotics added to cement should be tailored towards the causative organism, if preoperative cultures were successful in isolating the infecting organism and determining the antibiotic susceptibility [2]. Sukeik et al. concluded that the type of local antibiotics added to the cement or otherwise should be safe, thermostable, hypoallergenic, water soluble, have an adequate bacterial spectrum and be available as a sterile powder [3]. Kooet al. also suggested that antibiotics selected for cement spacer delivery should correspond to the sensitivity of the pathogens and be thermostable [4]. Nevertheless, novel delivery techniques may overcome this problem by microencapsulating antibiotics in alginate beads without affecting elution, handling properties and mechanical strength of the cement [5].

Even though there are no recommended diagnostic protocols adequate to exclude infection persistence prior to reimplantation, blood tests and synovial fluid aspiration before surgical treatment of PJIs can be helpful [2,3,6–10]. Aspirates are cultured and the results of microbiological diagnostics, including the causative organism and the specific antibiotic sensitivity, determine the treatment strategy where consultation of a microbiologist plays a crucial role [1,4,6,11–16].

Local antibiotic concentration at the site of infection can far exceed those obtained by systemic antibiotics alone and can remain well above therapeutic requirements for a longer period of time [1]. The objective is to deliver a high concentration of local antibiotics against the causative pathogens [2]. The choice of antibiotics is based on results of bacterial culture obtained from the preoperative aspiration or tissue specimens from around the joint [1,13,16]. Once the antibiotic susceptibility profile of the microorganisms is analyzed, a designated microbiologist should prepare a specific tailored combination of local antibiotics for use in the bone cement spacer [6], considering the patient allergy profile and medical conditions, particularly renal function [17,18]. If the infective organism cannot be identified preoperatively or infection is identified during a presumed aseptic revision, then a broad-spectrum empiric combination of antibiotics is used in an attempt to avoid development of resistance [1,2,13,15,19]. We have provided a list of all available antibiotics, the range of doses to be used in cement spacers and the organisms that they can target (Table 1).

TABLE 1. Available antibiotics and anti-fungals which can be used in spacers

Antibiotic Group	Type of Antibiotic	Activity Against	Dose per 40 gm cement (in grams)
Aminoglycoside	Tobramycin	Gram-negative bacteria such as *Pseudomonas*	1 to 4.8
Aminoglycoside	Gentamicin	Gram-negative bacteria-*Escherichia coli, Klebsiella* and particularly *Pseudomonas aeruginosa.* Also aerobic bacteria (not obligate/ facultative anaerobes)	0.25 to 4.8
Cephalosporin, 1st gen	Cefazolin	Gram-positive infections, limited gram-negative coverage	1 to 2
Cephalosporin, 2nd gen	Cefuroxime	Reduced gram-positive coverage, improved gram-negative coverage	1.5 to 2
Cephalosporin, 3rd gen	Ceftazidime	Gram-negative bacteria, particularly *Pseudomonas*	2
Cephalosporin, 4th gen	Cefotaxime	Gram-negative bacteria, no activity against *Pseudomonas*	2
Cephalosporin, 5th gen	Ceftaroilne	Gram-negative bacteria, no activity against *Pseudomonas*	2 to 4
Fluoroquinolone	Ciprofloxacin	Gram-negative organisms including activity against *Enterobacteriaciae*	0.2 to 3
Glycopeptide	Vancomycin	Gram-positive bacteria, including methicillin-resistant organisms	0.5 to 4
Lincosamide	Clindamycin	Gram-positive cocci, anaerobes	1 to 2
Macrolide	Erythromycin	Aerobic gram-positive cocci and bacilli	0.5 to 1
Polymyxin	Colistin	Gram-negative	0.24
β-lactam	Piperacillin-not available Piptzobactam	Gram-negative bacteria (particularly *Pseudomonas*), Enterobacteria and anaerobes	4 to 8
β-lactam	Aztreonam	Only gram-negative bacteria	4
β-lactamase inhibitor	Tazobactam	Gram-negative bacteria (particularly *Pseudomonas*), Enterobacteria, and anaerobes in combination with Piperacillin	0.5
Oxazolidinones	Linezolid	Multidrug-resistant gram-positive cocci such as MRSA	1.2
Carbapenem	Meropenem	Gram-positive and gram-negative bacteria, anaerobes, *Pseudomonas*	0.5 to 4
Lipopeptide	Daptomycin	Only gram-positive organisms	2
Antifungale	Amphotericin	Most fungi	200
Antifungal	Voricanazole	Most fungi	300-600 mg

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

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

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

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Authors: Valeriy Murylev, Matthew W. Squire, Lars Frommelt, Solmaz Saleri, Justin Greiner

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)