lence organisms treated with one-stage revision. IV antibiotics or IV followed by PO antibiotics are both reasonable options. However, there is no consensus on the antibiotic type and duration of antibiotic treatment. Presently, clinical judgement and normalization of infection labs (ESR and CRP) for six weeks, if elevated preoperatively, are helpful in determining the duration of antibiotic treatment.

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QUESTION 9: What is the optimal antibiotic treatment for culture-negative cases with positive clinical, radiographic or intraoperative findings for acute shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: The limited data suggests treatment should consist of an empiric antibiotic regimen recommended by an infectious disease specialist considering the local organism profile.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

The incidence of culture-negative PJI ranges from 5 to 34% [1]. The following predefined keywords were used during the search using Medline database: ("culture negative") AND ((prosthetic joint infection OR periprosthetic joint infection) OR (arthroplasty AND infection)). Nine original articles [2–11] and a single systematic review [12] have been published on the topic of culture-negative PJI. However, these studies have addressed culture-negative PJI of knee and hip arthroplasty, but not prosthetic shoulder or elbow infections, and have focused on outcomes of culture-negative versus culture-positive PJI (not on the best treatment). The existing publications indicate that the outcome of a patient with culture-negative PJI is similar to that of PJI with a pathogen identified. In these studies, most of these patients with culture-negative PJI have been treated with glycopeptides, mainly vancomycin. Previous antibiotic use was common in these patients, potentially confounding the ability to culture an organism [13].

In a large multicenter study of the microbial etiology of PJI that included more than 2500 PJI cases in Spain [14], Benito et al. analyzed the microbiology of 42 infections of shoulder arthroplasty (data not published); twenty-eight (66.7%) PJIs were caused by aerobic gram-positive cocci, mainly coagulase-negative Staphylococci, followed by *S. aureus*; nine (21.4%) were due to *Cutibacterium* spp. and another nine (21.4%) to *Enterobacteriaceae*; two cases were caused by *Pseudomonas* aeruginosa; five (11.9%) of the PJI cases were polymicrobial infections.

Given the limited nature of the available data, the antibiotic treatment recommended for culture-negative cases of acute shoulder PJI with positive clinical, radiographic or intraoperative findings remains unclear. It is recommended to work with an infectious disease consultant to arrive at a treatment strategy which includes, in addition to surgical irrigation and debridement with exchange of modular elements, empiric coverage against the most common pathogens of acute PJI. A broad-spectrum antibiotic regimen that covers aerobic gram-positive cocci (including methicillin-resistant *Staphylococcus aureus* and coagulase-negative staphylococci) and gram-negative bacilli, as well as *Cutibacterium* species, could be recommended. The need for antibiotic activity against specific multidrug-resistant microorganisms should be considered according to the patient's clinical and epidemiological background.

Treatment with vancomycin or teicoplanin or daptomycin would cover aerobic gram-positive cocci (mainly Staphylococci), in other words, 67% of infections according to the mentioned data. These antibiotics are also active against *Cutibacterium* spp.; however, a beta-lactam (penicillin or cephalosporins) would probably be more active than vancomycin according to a study of 28 strains of *C. acnes* isolated from shoulder surgery [15]. *C. acnes* is highly susceptible to a wide range of antibiotics, including beta-lactams, quinolones, clindamycin and rifampin [16]. However, resistance is beginning to emerge. Recent reports note an increasing emergence of resistance to macrolides, clindamycin, tetracycline and trimethoprim-sulfamethoxazole [16].

- Aerobic gram-negative bacilli would mainly include *Enterobacteriaceae* and *P. aeruginosa*. Besides of the coverture of aerobic gram-positive cocci (with vancomicin, teicoplanin or daptomicin), adding ceftriaxone would be a good option in order to additionally cover *Enterobacteriaceae*, (if there are no suspicion of mechanisms of *Enterobacteriaceae* acquired

resistance such as extended-spectrum beta-lactamases producing (ESBL) *Enterobacteriaceae*). Ceftriaxone is also very active against *Cutibacterium* spp. If *P. aeruginosa* is a concern, cefepime or ceftazidime (instead of ceftriaxone) should be considered. Meropenem (instead of a cephalosporin) would be an option if ESBL-*Enterobacteriaceae* are suspected; it also has activity against *P. aeruginosa*.

- Clearly knowing the organism and antibiotic susceptibility allows for the selection of an antibiotic which is maximally bactericidal to the specific pathogen and minimally toxic to the patient. However, in lieu of this data, the empirical treatment should be typically administered intravenously; the possibility of a second phase with oral antimicrobial treatment should be evaluated on a case by case basis. Consideration of antimicrobial coverage provided before the culture was taken could help to choose the antibiotic regimen, as the clinician may presume the preoperative antibiotic is effective and, theoretically, is the reason the bacteria did not grow in culture. The role of rifampin is not clear in the scenario of a culture-negative PJI, as it has demonstrated its efficacy only in the staphylococcal infections. Moreover, the emergence of resistance with rifampin is high if it is used without another simultaneous antibiotic to which the pathogen is susceptible, and this cannot be guaranteed in a culture-negative PJI.

Long courses of antimicrobial treatment are recommended for infections of hip (3 months) and knee (6 months) prostheses managed with debridement, antibiotics and implant retention (DAIR) [17]. Based on many observational studies and one clinical trial [18] most patients with acute PJI managed with DAIR may be safely treated for 8 weeks [13]. Available information on this topic refers to prosthetic knee and hip infections, and it remains unclear how this data applies to shoulder PJI, where the microbiology of infection varies compared with hip and knee.

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QUESTION 10: What is the optimal antibiotic treatment for culture-negative cases with positive clinical, radiographic or intraoperative findings for subacute or chronic shoulder periprosthetic joint infection (PJI)?

RECOMMENDATION: The limited data suggests treatment should consist of an empiric antibiotic regimen recommended by an infectious disease specialist considering the local organism profile.

LEVEL OF EVIDENCE: Consensus

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

RATIONALE

A systematic review was conducted in March 2018 using PubMed and Google Scholar databases. Keywords included "shoulder" AND ("prosthetic joint infection" OR "arthroplasty infection") AND ("culture" or "culture-negative"). After title and abstract review, fourteen studies were considered for inclusion; additional references were identified from review of reference lists.