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.

There are no studies that have reported clinical outcomes for culture-negative shoulder arthroplasty infections stratified by antimicrobials utilized. There are limited observational data on empiric antimicrobial treatment options for patients with non-shoulder arthroplasty infections. Antimicrobials for culture-negative infections should be selected in light of suspected organisms and their typical antimicrobial resistance profiles, drug tissue penetration (including bone penetration), bioavailability (if oral antimicrobials are selected), host factors (including comorbidities and allergies) and safety considerations. Prior antimicrobial exposure may inform organisms suppressed from culture growth. Additional considerations include the type of surgical procedure, such as whether hardware is retained or exchanged and the use of antimicrobial-laden cement. In the shoulder, most culture-positive subacute and chronic infections are due to coagulase-negative Staphylococci and *Cutibacterium* species [1–3]. Limited evidence in non-shoulder arthroplasty settings have reported good outcomes with vancomycin [4,5] and cephalosporins [5,6]. Most studies in the non-shoulder literature did not find culture negativity to be a poor prognostic factor [5–11], although one study [12] did find worse outcomes in culture-negative knees treated with irrigation and debridement.

The addition of rifampin may be considered if there is strong suspicion for gram-positive infection, particularly staphylococcal, in the setting of maintained hardware [13]. Synergy in the laboratory has been shown with rifampin for *Cutibacterium* [14]; however, there is insufficient clinical experience on the role of rifampin for the treatment of *Cutibacterium* infection to endorse its use [15]. Rifampin should never be used in monotherapy as resistance rapidly emerges; when employed rifampin should be used with careful monitoring and with full consideration of drug toxicities and drug interactions.

Prior antimicrobial exposure is a strong risk factor for culture-negativity [5,7,16]. When infection is suspected, antibiotics should be withheld prior to surgery whenever possible to reduce the likelihood of culture-negative infection. Whether a single dose of perioperative antimicrobial prophylaxis reduces the yield of organisms in low-burden infection is uncertain; two small randomized studies on hip and knee PJI suggest that a single dose of perioperative antibiotic therapy does not reduce operative culture yield [17,18]. Multiple operative samples should also be collected to increase the overall culture yield and to guard against placing too much emphasis on a single positive culture that, in some cases, may be a contaminant [19,20]. Aseptic inflammation and unusual organisms should also be considered in the differential of the culture-negative infection. In these cases, with concern for infection, pathology may be helpful to identify granulomas or other signs of atypical infection; thus, sending tissue samples for pathology is recommended to assist in properly interpreting any culture results. In the appropriate clinical and epidemiologic context, for example in immunocompromised hosts, and, in the setting of penetrating trauma, fungal and mycobacterial cultures should also be considered.

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