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QUESTION 8: What are the recommendations regarding the route (intravenous (IV) vs. oral (PO)) and length of postoperative antibiotic treatment when a one-stage revision arthroplasty is performed for subacute/chronic shoulder periprosthetic joint infection (PJI) caused by a virulent organism (e.g., methicillin-sensitive *Staphylococcus aureus* (*S. aureus*), or MSSA, vs. methicillin-resistant *S. aureus* (MRSA), E. coli)?

RECOMMENDATION: Intravenous antibiotics or intravenous followed by oral antibiotics are both reasonable options for one-stage revision shoulder arthroplasty for subacute/chronic shoulder PJI caused by a virulent organism. As there is no consensus on the route or duration, these treatment parameters should be selected in consultation with an infectious disease specialist.

LEVEL OF EVIDENCE: Limited

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

RATIONALE

Single-stage revision shoulder arthroplasty is an option for infected shoulder arthroplasty [1–4]. However, the outcomes depending on the virulence of the organism and the ideal duration and mode of antibiotic (IV or oral) treatment associated with single stage revision for PJI is not known.

For this purpose, a comprehensive search on PubMed and Embase database of all English literature till March 2018 was conducted to query keywords: (shoulder OR 'upper extremity') AND (arthroplasty OR replacement) AND (infection OR infected). A total of 1,434 articles were retrieved by the initial search. After review of the title and abstract of all studies, articles focusing on "management of infection" were extracted for further review (n = 31). After applying final exclusion ("two stage revision," "antibiotic spacer" or "antibiotic suppression") and inclusion criteria ("single stage revision," "antibiotic"), a full text review of the articles was conducted, and 6 articles were selected for final analysis. Articles reporting single stage revision but without any information on antibiotic type and or duration were further excluded (n = 2).

The selected studies for analysis (n = 4) evaluated the role of postoperative antibiotic therapy for single stage revision shoulder arthroplasty for PJI. However, it must be emphasized that these studies did not stratify results by the virulence of the organism. Thus, no firm conclusions regarding treatment according to the virulence of the organism can be made.

Beekman et al. retrospectively reviewed 11 consecutive patients with an infected reverse shoulder arthroplasty who underwent single stage revision arthroplasty [5]. Two of these patients had monobacterial infection with a virulent organism (*Staphylococcus aureus* and *Escherichia coli*). Both of these patients received at least three days of IV antibiotic and were discharged on oral antibiotics, which were continued for at least three months. Ince et al. retrospectively reviewed 16 patients with an infected shoulder arthroplasty (three with identified virulent organisms) that underwent single stage revision shoulder arthroplasty [6]. Three patients (~19%) had undergone revision surgery prior to review. All patients received intravenous antibiotics for mean of 8.6 days (range: 5-14 days) and antibiotics were stopped when the surgical incision had healed and/or infection labs (erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and white blood cell (WBC) count) were down trending. No recurrence of infection was reported in 9 patients that were reviewed. Klatte et al. reported their results of single stage revision shoulder arthroplasty for PJI in 35 patients, of which 26 were available for review [7]. Patients received IV antibiotics for a mean of 10.6 days (range: 5-29 days), and 11 patients received PO antibiotics for a mean duration of 12.8 days (range: 5-24 days). There were two recurrences. Cuff et al. retrospectively reviewed 22 infected shoulder arthroplasties of which 11 were treated with single stage revision to reverse shoulder arthroplasty and intravenous antibiotics [8]. Five of the 10 patients had virulent pathogens. Patients received antibiotics for 2 (1 patient) or 6 (4 patients) weeks depending on cultures and intraoperative histology results. There was one recurrence of infection.

There is little evidence regarding the subsequent antibiotic management of subacute and chronic shoulder PJI due to high viru-

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