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QUESTION 7: What is the optimal antibiotic therapy in cases of culture-negative (CN) periprosthetic joint infections (PJIs)?

RECOMMENDATION: In patients with true CN PJIs, the antibiotics should be selected to have broad spectrum activity against both gram-positive and gram-negative organisms. In addition, the exact choice should relate to the known modern epidemiology in that country.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 87%, Disagree: 6%, Abstain: 7% (Super Majority, Strong Consensus)

RATIONALE

In the literature, rates of CN PJIs vary from 0-42% but reports suggest that the outcomes are not necessarily worse than for culture positive cases if rigorous and robust pathways for diagnosis and management are followed [1–7]. Factors associated with increased risk of culture negativity include prior antibiotic use, delay in transportation of the samples to the laboratory and variations in culture techniques, including short duration of culture [1,8–11]. It is important to note that several studies demonstrate that administration of antibiotic prophylaxis prior to obtaining culture samples did not interfere with isolation of the infecting organism [12].

A recent systematic review by Yoon et al. evaluated clinical studies related to culture-negative PJI. After exclusions, seven studies were included in the analysis, with all studies being retrospective [1,4,6–8,12–15]. Of these, four studies defined PJI using MusculoSkel-

etal Infection Society (MSIS) criteria [6,13–15]. In the majority of these studies glycopeptides, such as vancomycin, were used followed by cephalosporins, beta-lactams, quinolones or combination therapy. The duration of intravenous antibiotics for CN PJI was usually six weeks. The investigators also noted that the use of antibiotics for CN PJI was accompanied with appropriate surgery, stating that the choice of surgical strategy greatly affects the treatment results of PJI. Most of the included studies reported that two-stage arthroplasty followed by 4-6 weeks of antibiotic therapy was effective with a success rate of 70-100%. Six of the seven studies in this review demonstrated similar success rates between culture-positive (CP) and CN PJI, with one reporting greater success for CN PJI [1,4,6–8,13–15]. The authors of the systematic review recommended that further studies are required to determine optimal therapy for patients with CN PJI. The latter systematic review did not include studies that have demonstrated a suboptimal outcome for patients with CN PJI [16–18].

A few recent studies have attempted to further explore the issue of CN PJI. Kang et al. reported on the challenges of selecting the appropriate antibiotics and the treatment of CN PJI was commenced with cefazolin and changed to glycopeptides if infection did not respond to the initial treatment [18]. Wang et al. also reported on the challenges of treatment for CN PJI [17]. They utilized intravenous vancomycin and/or an aminoglycoside for two weeks followed by an oral antibiotic such as levofloxacin and rifampin for an additional four weeks. A cement spacer containing vancomycin/meropenem was used in their cohort. In another study Peel et al. reported the use of vancomycin and cephalosporin followed by a broad spectrum oral combination comprising fusidic acid, rifampin +/- ciprofloxacin for a median of 7 months (3-20 months interquartile range) in the majority of the patients but choice of regimen varied by presentation [9].

In 2013 Marschall et al. published a survey in which members of the Emerging Infections Network were asked about current treatment of PJI. Regarding CN PJI, the vast majority of the responders chose a two-drug regimen in hip and knee infections, most commonly using vancomycin with ceftriaxone or vancomycin with oral fluoroquinolone as upfront antibiotic treatment [19].

In summary, it appears that the rate of CN PJI varies vastly from one study to another, perhaps reflecting the variability in definition of PJI, differences in culture techniques and the local epidemiology. Despite the presence of some studies demonstrating acceptable outcomes for CN PJI, the selection of optimal antibiotics for these cases remains challenging. The majority of reported series utilize a combination of antibiotics in the CN PJI. In an effort to reduce financial and psychological costs associated with optimal management of CN PJI, all efforts should be made to isolate the infecting organism. Similar to culture-negative endocarditis, zoonotic agents such as *Coxiella, Brucella, Bartonella* and *T. whipplei* are not easily detectable by the usual means and are not treated by common empirical agents such as glycopeptides [20]. A recent study has demonstrated that next generation sequencing (NGS) has a promising role in isolating the infecting organism in up to 90% of CN PJI cases [21]. Based on the emerging data, consideration should be given to the use of NGS or other molecular techniques in isolating of the infecting organism in patients with CN PJI. Serologies or serologic markers for certain zoonotic and endemic fungal infections should also be considered in the appropriate context.

If all attempts to isolate the infecting organism fail, then strategies employed in choosing an antibiotic regimen for CN PJI must be individualized based on risk factors, previous history and knowledge of the local epidemiology. The antibiotic treatment of CN PJI usually includes broad spectrum antibiotics with a prolonged intravenous phase. Glycopeptides play a pivotal role but consideration should be given to the use of multiple-drug regimens.

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