HK94: What is the optimal antimicrobial treatment for patients with culture-negative PJI?

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Response/Recommendation:

For treatment of CN PJI, the antibiotics should be selected to have a broad-spectrum activity against both gram-positive and gram-negative organisms. Consideration should be given to a combination or multiple drug regimens including a glycopeptide e.g. vancomycin. The regimen choice should be individualized based on risk factors, previous history and knowledge of the local epidemiology.

Level of Evidence: Weak

Delegate Vote:

Rationale:

While identifying the causative microorganism is central to the management of PJI, a substantial proportion of cases, culture-negative (CN) PJI fail to yield identifiable pathogens during routine microbiological testing. The reported prevalence of CN PJI ranges from 5% to 42%, reflecting variations in diagnostic protocols, patient populations, and laboratory methodologies. [1][2][3] This lack of microbiological confirmation poses challenges in choosing effective antimicrobial therapies, increasing the reliance on empirical and often broad-spectrum treatment regimens.

Management of CN PJI after knee and hip arthroplasty generally requires a multidisciplinary approach involving surgical intervention and antimicrobial therapy. Empirical antimicrobial therapy for CN PJI commonly includes broad-spectrum intravenous antibiotics, such as vancomycin for Gram-positive coverage and cephalosporins or fluoroquinolones for Gram-negative pathogens. This is typically followed by long-term oral therapy with agents like rifampin and levofloxacin. [1] [2] [4] The use of local antibiotic delivery, through antibiotic-impregnated cement spacers or beads, complements systemic therapy by achieving high local drug concentrations and reducing systemic toxicity. [1] [3] Despite these strategies, the lack of pathogen-specific guidance often results in longer treatment durations, increased risk of adverse drug reactions, and uncertainty about treatment efficacy.

Current evidence suggests that CN PJI outcomes are comparable to those of culture-positive PJI when robust treatment protocols are employed. [3] [5] However, significant gaps persist in standardizing diagnostic and therapeutic approaches. Molecular diagnostic methods and multidisciplinary care are essential to advancing the management of CN PJI. This article reviews existing literature to explore the treatment strategies for CN PJI after knee and hip arthroplasty, with a focus on antimicrobial interventions and their respective outcomes.

We included 25 studies in our final analysis.[2-4, 6-27] All studies are retrospective cohort studies. Most studies reported culture-negative PJIs in both hip and knee arthroplasties. Cultures were obtained during one-stage or two-stage, resection arthroplasty or even amputations. Tan et al. 2018 was the largest cohort (N=219). They identified the prevalence of suspected culture-negative PJIs as 22% and according to the modified criteria of the Musculoskeletal Infection Society (MSIS), the prevalence was 6.4% [3]. The prevalence of CN PJIs can be minimized with adequate culturing techniques [6]. Studies reported preoperative administration of antibiotics in

nearly 53 to 68% of culture-negative periprosthetic joint infections (CN PJIs) [2][4][7][8][9][10]. Berbari et al. reported a decrease in the number of CN PJIs with an increase in the duration of antibiotic-free intervals prior to the sampled culture [2].

The most used postoperative antibiotics were cephalosporins (8-85%), vancomycin/Teicoplanin (7-70%), quinolones (3-7.4%), Aminoglycosides (e.g. gentamicin) (7%), a combination of antibiotics (7%) and others e.g. linezolid, piperacillin-tazobactam, meropenem, cefoperazone–sulbactam, rifampicin. The antibiotic regimen started with a duration of parenteral therapy (2-6 weeks) followed by another duration of oral therapy (12 weeks). The PJI recurrence rate in these studies ranged from 9 – 30.7% at follow-up ranging from 1 to 5 years [2][4][7][8][9][10][11].

Studies by Ji et al. evaluated the role of adding an intra-articular antibiotic infusion to the systemic regimen of IV vancomycin given for a mean of 14 days. They added an intra-articular infusion of 0.5 g imipenem and 0.5 g vancomycin alternately used in the morning and afternoon. This procedure is repeated for 16 days. This intra-articular infusion treatment was guided by serum and synovial markers. They reported that intra-articular vancomycin infusion avoided the systemic toxicity of its intravenous use and reached a higher levels in the joint space, especially in immunocompromised patients and patients with fungal infections [12][13].

A few studies have compared the results of treatment of CN PJIs to culture-positive PJIs and showed comparable PJI recurrence rate and good prognosis in treatment of CN PJIs with a similar regimen of 1st generation cephalosporin/glycopeptide (e.g. vancomycin or Teicoplanin) [11][14][19][20][22]. All studies reported lower serum markers in CN PJIs at the time of presentation and a shorter time required for normalization with treatment. Many reports have chosen the broad spectrum glycopeptide vancomycin as the first choice in the treatment of CN PJIs with no recurrence rate and high success rate with less complication rate [4][28]. Reports also attributed the wide use of vancomycin in the treatment of CN PJIs to the recent high prevalence of MRSA and MRSE infection [13]. However, the prolonged use of broad-spectrum glycopeptide antimicrobials for extended periods requires further investigation and studies [14]. Anti-fungal coverage has been rarely described owing to side effects of antifungal medicines. Li et al have mentioned the use of Meropenem and Caspofungin intra-operatively in two-stage revision surgeries of CN-PJI patients. [15]

Prolonged treatment of PJIs with empirical broad-spectrum antibiotics especially vancomycin and the piperacillin-tazobactam combination has been associated with high renal and other complications [29]. The rate of antibiotic-related complications has been shown to be significantly higher in CN PJIs reaching 59% compared to 11.3% in CP PJIs.

Recent developments in molecular techniques, like next generation sequencing (NGS), hold promise for identification of causative pathogens in CN PJI patients and delivery of targeted antimicrobial treatment with the potential to reduce the rate of antibiotic-related complications [17][18][30]. In a study by Wang et al. NGS helped the identification of pathogens in CN PJI patients, allowing a targeted antibiotic treatment against a specific pathogen that had a lower antibiotic complication rate and a lower cost compared to the empirical antibiotic-treated group [16]. Also, sonication of implants and disruption of biofilm in patients with CN PJI has also been proposed as a strategy to help identify the organisms allowing removal of biofilm and proper microbe identification [3]. On the other hand, positing the high success rate of treatment of CN PJIs, some investigators have argued against the use of expensive technologies like gene sequencing in patients with CN PJIs, and advocated for broad spectrum empirical antimicrobial treatment [10]. The regimen choice should be individualized based on risk factors, previous

history and knowledge of the local epidemiology [31],and should be discussed in a multidisciplinary team including orthopaedic surgeons, medical microbiologists and infectious disease specialists.

Conclusion:

The optimal management of patients with CN PJI remains challenging and elusive. The antibiotics should be selected to have a broad-spectrum activity against both gram-positive and gram-negative organisms. Consideration should be given to a combination or multiple drug regimens including a glycopeptide e.g. vancomycin which plays a pivotal role and may provide a higher success rate in the treatment of CN PJI. However, with the expanding menu of organisms causing CN PJI, including fungi and atypical pathogens, the role of molecular techniques for identification of causative pathogen and targeted antimicrobial delivery may be justified. In addition, the regimen choice should be individualized based on risk factors, previous history, knowledge of the local epidemiology and should be discussed in a multidisciplinary team including orthopaedic surgeons, medical microbiologists and infectious disease specialists.

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