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QUESTION 6: When should rifampin be added to the regimen of antibiotics for management of patients with periprosthetic joint infections (PJIs) undergoing surgical treatment?

RECOMMENDATION: Rifampin should be considered in the treatment of staphylococcal PJIs in patients managed surgically with debridement, antibiotics and implant retention (DAIR) or single-stage exchange where activity against biofilm is required. Rifampin should only be used in combination therapies, with the best reported combination appearing to be with a fluoroquinolone.

LEVEL OF EVIDENCE: Moderate

DELEGATE VOTE: Agree: 96%, Disagree: 2%, Abstain: 2% (Unanimous, Strongest Consensus)

RATIONALE

The excellent efficacy of rifampin against biofilm produced by staphylococci has been shown in vitro, in animal models and in patients with orthopaedic implant-related infections undergoing DAIR [1–8]. Nevertheless, rifampin should be used with care because of the danger of rapid emergence of resistance and potential unwanted effects, such as severe nausea, hepatotoxicity, interstitial nephritis and cytopenia [9,10]. Rifampin is a potent inducer of the cytochrome P450 oxidative pathway and can result in significant drug interactions [10,11]. Monotherapy is known to quickly promote rifampin resistance and must therefore be avoided [12,13]. The emergence of rifampin resistance in *S. aureus* is of particular concern [8,14]. The best documented combination partners for rifampin are fluoroquinolones [15,16].

Clinical data supporting the use of combination rifampin antimicrobial therapy and surgical debridement for the treatment of staphylococcal PJIs are available [14,17]. Widmer et al. showed in an open-label study that 9 of 11 patients (82%) with staphylococcal or streptococcal PJIs that could not undergo removal of hardware were successfully treated with rifampin in combination with either a beta-lactam or with ciprofloxacin [1]. A randomized controlled study by Zimmerli et al. showed that among 24 patients with methicillin-susceptible *Staphylococcus aureus* (MSSA), or coagulase-negative staphylococcus (CNS)-PJI, with stable implants and a short duration of infection managed with DAIR. Those able to tolerate long-term (three to six months) combination therapy with ciprofloxacin-rifampin achieved cure at higher rates than those treated with a ciprofloxacin-placebo [15].

Trebse et al. followed 24 patients with PJIs and retained implants prospectively over 4 years, showing 83% with a successful outcome. A total of 17 of the patients had Staphylococcal infections, and were treated with rifampin combination therapy; two of the four patients who failed had staphylococcal infections, one with methicillin-resistant *Staphylococcus aureus* (MRSA) and one with CNS [17].

Retrospective case series have described the success of rifampin combination therapy [10,14]. Successful treatments with rifampin-fluoroquinolone therapy was shown by Berdal et al. and Barberan et al. [19,20]. Rifampin, in combination with other antibiotics, including fusidic acid, vancomycin or daptomycin, has also been reported to be effective [21-23]. Many of the reported case series primarily address the successful treatments of MSSA and CNS infections. Barberan et al. observed a non-significantly ($p = 0.08$) higher failure rate in 7 MRSA-infected, as compared to 14 MSSA-infected patients. More important, in patients with a duration of infection ≤ 1 month treated with levofloxacin plus rifampin, the outcome was significantly better than that for patients with a longer duration of infection [24]. A cohort study by Peel et al. included 43 methicillin-resistant Staphylococcal infections (24 MRSA) and found 86% of patients were treated successfully, most with rifampin-fusidic acid. The found eight out of nine failures were in MRSA cases [25]. A retrospective multicenter study by Lora-Tamayo et al. reported on 345 *S. aureus* PJIs managed with joint retention, including 81 MRSA cases. A total of 88% of patients received rifampin combination therapy and failure rates were similar in MRSA (46%) and MSSA (44%) cases [26].

The Infectious Diseases Society of America (IDSA) PJI and MRSA management guidelines recommend the use of rifampin combination therapy (2-6 weeks of pathogen specific IV antimicrobial therapy plus rifampin followed by 3-6 months of rifampin plus an oral companion drug) in the treatment of staphylococcal PJIs/hardware infections in patients managed with debridement or single-stage exchange [27,28]. European guidelines include similar recommendations [29].

Unanswered questions regarding the role of rifampin remain; however, many clinical studies have focused on rifampin-quinolone combinations, with little information available for beta lactam-rifampin therapy. Of note, fluoroquinolone-resistant Staphylococci are found in many settings, especially in MRSA-strains [30]. The emergence of rifampin resistance can occur even when using combination therapies [8,25,26,31]. Drug interactions lowering the serum concentrations of companion antimicrobials, including fusidic acid and clindamycin, have been reported [32,33]. The clinical significance of these interactions, however, is still unknown. Additionally, the optimal duration of combination antimicrobial therapies, including rifampin, for the treatment of prosthetic joint infections with retained hardware is not yet known. While extended treatment (3-6 months) is recommended and often used, shorter treatment courses may be as effective in some settings [34].

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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-