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QUESTION 8: What antibiotic therapy and duration of treatment should be used in Enterococcal periprosthetic joint infections (PJIs)?

RECOMMENDATION: Based on the limited available evidence, combination antimicrobial therapy should be considered for the treatment of Enterococcal PJIs, at least during the first weeks of treatment. Antibiotics should be tailored according to the susceptibility of the infective microorganism.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 85%, Disagree: 9%, Abstain: 6% (Super Majority, Strong Consensus)

RATIONALE

Enterococci are often part of polymicrobial infections [1,2], have the ability to form biofilms [3,4] and thus can be difficult to manage [5]. *Enterococcus faecium*is listed as one of the ESKAPE (an acronym for *Enterococcus faecium, S. aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacter spp.*) organisms, which are resistant to a majority of antibiotics available in our arsenal [6,7].

There is a lack of high quality randomized, controlled, prospective comparative treatment studies. However, based on the high failure rate of Enterococcal PJIs and the known limited bactericidal activity of ß-lactams on enterococci, some authors have suggested the use of combination antibiotic therapy for management of patients with enterococcal PJIs [8]. However, another study demonstrated that patients who received monotherapy had the same outcome as those treated using combination therapy regimen [9]. El Helou et al. described an 80% success rate using debridement, retention of the implant and intravenous ampicillin with or without gentamicin [9]. The success rate was similar in the monotherapy and combination groups, but nephrotoxicity was significantly higher among those receiving aminoglycosides. The results of the multi-institutional study by Kheir et al. support the former recommendation of combination systemic therapy [1]. Although the authors did not find statistical significance, there was a trend toward higher treatment success with combination antibiotic therapy. In addition, there is a high risk of selection bias in retrospective studies evaluating the efficacy of antibiotic therapy, as dual therapy is often applied in more severe infectious cases. The efficacy of dual theraphy in Enterococcal infections in clinical studies is primarily demonstrated for Enterococcal endocarditis. For monomicrobial non-resistant *E. faecalis* and *E. faecium* PJI, we recommend a combination of an intravenous cell wall synthesis-inhibiting agent (ampicillin or vancomycin, respectively) and to add gentamicin as a synergistic antibiotic, at least during the first two weeks of treatment, which is concordant with previous literature [1,5,10,11]. It is important to note that administration of a systemic aminoglycoside can increase the risk of nephrotoxicity and ototoxicity [9]. Other alternatives suggested in the literature to include as a synergistic antibiotic (instead of gentamicin) are ceftriaxone [12] or daptomycin [13-15]

Interestingly, it has also been suggested that rifampin in combination with other antibiotics may also lead to a lower rate of failure in early Enterococcal PJIs. Tornero et al. found that the administration of rifampin combined with other antibiotics was associated with a lower rate of failure than alternative antibiotics [16]. In addition, recent in vitro data showed that linezolid or ciprofloxacin combined with rifampin had better activity against Enterococcal biofilms than ampicillin or ampicillin plus rifampin; therefore, these combinations are potential alternatives [17].

Emerging antibiotic resistance, specifically to vancomycin, is a challenging problem for the management of Enterococcal PJIs [5,18]. Plasmid-mediated resistance to vancomycin was first described in 1986, and shortly thereafter numerous reports of the vancomycin-resistant *Enterococcus* (VRE) species appeared in the literature [19]. VRE species are phenotypically and genotypically heterogeneous, and among all of these phenotypes and genotypes, VanA resistance phenotype has been most commonly investigated [19]. For VRE, the literature suggests the use of either linezolid (with or without rifampin) [17] or daptomycin [1,20]. Although linezolid-resistance has been reported, fortunately at present there is no report of emerging daptomycin-resistant *Enterococcus* [21–24].

Polymicrobial infections are challenging to treat, as administration of multiple antibiotics is often needed [25]. For polymicrobial infections, broad-spectrum coverage should be performed. Literature is sparse on the use of oral antibiotics for patients with polymicrobial enterococcal PJIs, and it is not known if oral antimicrobial can be used for successful treatment of these patients.

The review of the available literature revealed that there was a high variability of antibiotic treatment duration for Enterococcal infections and lack of analysis regarding treatment duration in the above studies. In the study by Kheir et al., each patient's antibiotic duration was listed, and the majority of patients had six weeks of antibiotic treatment (although the range was broad: from 4-36 weeks of duration) [1]. Duijf et al. reported three months of antibiotic treatment resulting in 66% of patients retaining their implants [26]. This may suggest that longer antibiotic treatment may be beneficial in Enterococcal PJIs;however, further study is warranted in this domain.

Based on the available literature, and our experience, we recommend that patients with Enterococcal PJIs should be treated with 6-12 weeks of antimicrobial agents, preferably in combination.

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QUESTION 9: What are the indications for utilizing fosfomycin, tigecycline and daptomycin, either instead of other antibiotics or in conjunction with other antibiotics, for the management of periprosthetic joint infections (PJIs)?

RECOMMDENATION FOR DAPTOMYCIN: Daptomycin is an alternative treatment for patients with PJIs caused by methicillin-resistant *Staphylococcus aureus* (MRSA).

LEVEL OF EVIDENCE: Moderate

RECOMMENDATION FOR FOSFOMYCIN: Although there is no clinical experience using fosfomycin in PJIs, it could be considered in infections due to multi-drug resistant gram-positive (MDR-GP) or gram-negative bacteria (GNB) as a part of a combination regimen with daptomycin, rifampin or tigecycline when the microorganism is susceptible.

LEVEL OF EVIDENCE: Limited

RECOMMENDATION FOR TIGEYCYLINE: Tigecycline could be considered for the treatment of MDR-GP or -GNB as a part of a combination regimen when the microorganism is susceptible.

LEVEL OF EVIDENCE: Limited

DELEGATE VOTE: Agree: 86%, Disagree: 4%, Abstain: 10% (Super Majority, Strong Consensus)

RATIONALE

Daptomycin

Daptomycin is a cyclic lipopeptide with concentration-dependent bactericidal activity against gram-positive microorganisms. It is highly active against *Staphylococcus aureus*, coagulase-negative Staphylococci, *Enterococcus faecalis* and *Enterococcus faecium*, including both planktonic and biofilm-embedded bacteria [1]. Daptomycin combined with gentamicin has been shown to have synergistic activity on intracellular *S. aureus*. Additionally, daptomycin seems to exhibit activity against the stationary-phase bacteria inside a biofilm [2–4]. Several animal models of foreign-body infection demonstrated a high success rate with daptomycin but always in combination with rifampin [5,6].

Since its commercialization, several case series and one clinical trial have evaluated the efficacy of daptomycin in PJIs (Table 1). The first description [7] included 12 patients that received 4 mg/kg of daptomycin in monotherapy with a success rate of 45.5%. In addition, out of the five patients considered a success, only one retained the implant with oral suppressive therapy. Byren et al. [8] performed a