G82: What is the optimal antimicrobial treatment for patients with orthopedic infections caused by Enterococci?

Alisina Shahi, Craig Aboltins, Kenneth Mathis, Marjan Wouthuyzen-Bakker, Staffan Tevell, Renjy Nelson, Abdullah Hammad, Seung-Hoon Baek, Belen Comeche, Cecile Ronde-Oustau

Response/Recommendation:
Optimal antimicrobial treatment for patients with Enterococci infections include ampicillin or ampicillin/ceftriaxone combination for ampicillin susceptible enterococcal infections, while vancomycin can serve as the first-line treatment for ampicillin resistant Enterococci or in the setting of penicillin allergy. Daptomycin and linezolid are options for vancomycin resistant Enterococci (VRE) or when vancomycin cannot be used.

Level of Evidence: Limited

Rationale:

Orthopedic infections caused by *Enterococcus faecalis* and *Enterococcus faecium* are linked to significant morbidity due to their ability to effectively form biofilms, their intrinsic resistance to commonly used antimicrobials such as cephalosporins and increasing prevalence of vancomycin-resistant enterococci (VRE). Up to 64% of *enterococcus*-related PJIs involve other pathogens, complicating treatment. [1] Only relatively small, retrospective observational studies evaluating antimicrobial therapies for enterococcal bone and joint infection are available. [2–9] These studies are largely non-comparative, meaning definitive evidence-based recommendations about the superiority of particular regimens cannot be made.

Ampicillin susceptible Enterococci (intravenous treatment):
Most isolates of *E. faecalis* and some *E. faecium* isolates are susceptible to intravenous ampicillin/penicillin and these antibiotics would be considered the standard of care for most infections. However, there has been some interest in combination therapies to improve the outcomes for certain difficult treat enterococcal infections, particularly in implant related infections. The combination of ampicillin and ceftriaxone has demonstrated synergy in treatment of ampicillin susceptible enterococcal endocarditis and in *in vitro* checkerboard studies. This synergy is attributed to the fact that each drug had different penicillin-binding proteins (PBPs) as targets (amoxicillin, partially saturated PBP 4 and 5; ceftriaxone, PBP 2 and 3), thus improving the bactericidal effect. However, this effect is likely to be attenuated significantly when ceftriaxone MIC is high which limits its use with penicillin [10] as well as in biofilm infections, as the synergy is seen largely in the exponential growth phase of bacteria and markedly less in the stationary phase [11]. Although good outcomes have been reported in one small study, there are no comparative studies examining the advantages of this combination therapy over ampicillin or penicillin alone [11–13].
Ampicillin combined with an aminoglycoside has historically been regarded as a beneficial regimen for treating ampicillin susceptible enterococcal infections due to its bactericidal synergy. Ampicillin disrupts bacterial cell wall synthesis, allowing aminoglycosides to penetrate the cell and inhibit protein synthesis, leading to rapid bacterial elimination. Despite its effectiveness, the

emergence of high-level aminoglycoside resistance as well as aminoglycoside related nephrotoxicity and ototoxicity has significantly limited its clinical utility, particularly in patients with underlying renal dysfunction. The synergistic bactericidal activity of aminoglycosides may be highly compromised in the setting of orthopedic infections with local purulence, acidic pH, and under anaerobic conditions [14,15].
Although clinical studies supporting the use of dual therapy are lacking, it may be considered from an in vitro point of view and the relatively high relapse rates observed in enterococcal infections, in particular in the first weeks after surgical debridement and in those patients in whom the implant will be retained.

Ampicillin resistant Enterococci (intravenous treatment):
Vancomycin remains a cornerstone in the treatment of ampicillin resistant enterococci. Its mechanism involves inhibiting cell wall synthesis in Gram-positive bacteria. However, its efficacy diminishes significantly in biofilm-associated infections, where enterococci demonstrates increased tolerance [16–20]. Biofilms create a protective environment, reducing vancomycin penetration and activity, leading to suboptimal outcomes.
Dalbavancin may be a good alternative option as it demonstrates better activity within biofilm [29]. It has bactericidal action, and its activity relies on disrupting bacterial cell membranes. However, clinical data to support its use in enterococcal infections is lacking, and it has not been shown to have advantages over other antimicrobials in bone and joint infections. Furthermore, EUCAST has not provided breakpoints for daptomycin in enterococcal blood-stream infections due to insufficient evidence [21], and high doses are required to achieve a probability of target attainment above 50%. [22] Thus, careful monitoring to mitigate the risk of myopathy and eosinophilic pneumonia is required.[6,12,13, 30].

Vancomycin resistant enterococci (VRE)
VRE strains, particularly *Enterococcus faecium*, often carry the *VanA* or *VanB* resistance genes, which confer resistance to both vancomycin and teicoplanin (especially *VanA*). While some *VanB* strains may retain susceptibility to teicoplanin, its clinical efficacy is unreliable, and it is not considered a first-line treatment for VRE infections.
Daptomycin retains activity *in vitro* against VRE and may have activity in biofilm-associated infections, even though there is a risk of emergence of resistance during therapy. Linezolid is another option for VRE infections, with the advantage of providing an oral option. Initial combination therapy may be considered [22]
Pristinamycin is an oral streptogramin antibiotic that demonstrates activity against many isolates of Enterococcus faecium, including vancomycin-resistant strains (VRE), but not Enterococcus faecalis. There are a limited number of studies reporting reasonable outcomes, mostly being used as chronic suppression, for orthopaedic infections caused by Gram-positive organisms, including enterococci [33].

Duration of treatment and oral switch
For this recommendation we have not focused on the duration of antibiotic treatment and the timing for an oral switch. In our knowledge there are no studies supporting a longer duration of treatment for enterococcal PJIs compared to other microorganisms. An early switch to oral antibiotics can be considered in cases in which an oral antibiotic is available with a good bioavailability, which in general is not the case for betalactam antibiotics, like amoxicillin. For

this reason, we recommend an IV period of at least two weeks before switching to oral, provided that the patient has a good clinical recovery.

Oral follow-up

Comparative data on oral follow-up treatment is lacking. Amoxicillin or linezolid are potential options highlighted in recent recommendations [25] . EUCAST has not provided breakpoints for amoxicillin in bone and joint infections as there are concerns on the probability of target attainment within the wild-type population. Based on PK modelling, a dosing of 750 mg x4 is preferred[26].

Linezolid inhibitis bacterial protein synthesis, and has excellent oral bioavailability. However, prolonged use is limited by side effects such as cytopenias, optic neuritis and irreversible peripheral neuropathy, the risk of which increase with cumulative dose. As there is an interindividual variability in serum levels of linezolid, it requires regular monitoring to mitigate toxicity [31]. Limited retrospective, non-comparative data shows reasonable outcomes in bone and joint infections caused by enterococcus [14-17, 32]. Despite the challenges, linezolid remains a valuable option in the treatment arsenal for orthopedic infections caused by enterococci.

Rifampin-based regimens

Rifampin is widely used in the management of staphylococcal biofilm-related orthopedic infections due to its activity against biofilm-associated bacteria. EUCAST has not provided breakpoints for rifampin in enterococci, and *in vitro* data on rifampin activity when combined with other agents against biofilm-associated enterococcal infections is conflicting. There is no clinical evidence to support the addition of rifampin in the treatment of enterococcal bone and joint infections [1,27–30].

Enterococci as part of a polymicrobial infection

Polymicrobial infections involving *Enterococcus* are notably challenging and are associated with significantly higher failure rates compared to monomicrobial infections. A substantial proportion of enterococcal infections, particularly in PJIs, are polymicrobial, further complicating treatment. The coexistence of multiple pathogens creates a synergistic environment that enhances biofilm formation, reducing the effectiveness of standard therapies. Consequently, accurate identification of all infecting organisms is crucial to tailor antibiotic regimens effectively and improve the likelihood of treatment success. In such complex scenarios, combination therapies are frequently necessary to address the diverse microbial population and improve the likelihood of treatment success. Definitive therapy must be guided by the susceptibility profile to optimize outcomes and combat resistance.[31–33]

Conclusion

Optimal treatment for enterococcal PJIs demands a multidisciplinary approach integrating antibiotic regimens and surgical interventions. There is a lack of high-quality clinical evidence to recommend specific antimicrobial treatments over others and choices should be guided by antimicrobial susceptibility testing and patient factors. Ampicillin or penicillin remain first line intravenous treatment options for treatment of ampicillin susceptible enterococci, Initial combination therapy with ampicillin/ceftriaxone may be considered in select situations even

though the evidence is limited. Vancomycin can be used for ampicillin resistant enterococci or in the setting of penicillin allergy or intolerance. Daptomycin and linezolid are valid options in the treatment for vancomycin resistant enterococococci. Amoxicillin or linezolid may be considered for oral follow-up. Future research should prioritize the development of biofilm-disrupting therapies, innovative combination regimens, and strategies to address emerging resistance, ultimately improving patient outcomes in these challenging infections.

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