



## The Enterococci : a Continuing Therapeutic Challenge

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**E**nterococci are often referred to as second rate pathogens because they most commonly cause infections in patients who have been on multiple antibiotics, have been hospitalized for prolonged periods of time, and/or have severe underlying diseases. It should be remembered, however, that enterococci (primarily *Enterococcus faecalis*) have long been recognized as a cause of infective endocarditis, ranking third behind streptococci and staphylococci and accounting for five to fifteen percent of cases in series dating back to the early 1900s. More recently, enterococci have been reported as the second most common cause of nosocomial endocarditis. Prior to the emergence of vancomycin resistance, the major therapeutic problem posed by enterococci was the lack of bactericidal activity, that is, the inability of a single antibiotic to reliably kill enterococci. This is the likely explanation for the inability of penicillins or vancomycin given as monotherapy to cure enterococcal infective endocarditis. In the 1950s, it was recognized that the combination of a cell wall active agent with an aminoglycoside (such as streptomycin) markedly enhanced the cure rate for enterococcal infective endocarditis and it was also observed that this combination resulted in a bactericidal effect and *in vitro* synergism. With the subsequent emergence of high-level resistance to streptomycin, other aminoglycosides were used with success. In the early 1980s, enterococci with high-level resistance to streptomycin and gentamicin were described; the gene responsible for high-level gentamicin resistance (*aac(6')*/*aph(2'')*), found also in staphylococci, was found to cause not only high-level resistance to gentamicin but also high-level resistance and/or resistance to synergism with all other commercially available aminoglycosides with the exception of streptomycin (an aminocyclitol). While the aminoglycoside arbekacin (available in some countries) may have activity against some highly gentamicin resistant strains, clinical data with this compound for enterococcal endocarditis caused by highly resistant strains are generally lacking. Additional aminoglycoside modifying enzymes that confer high-level resistance to gentamicin but may spare one or another aminoglycosides have been described in the United States; unfortunately, many clinical isolates have multiple aminoglycoside modifying enzymes which will often be active against such spared compounds.

With the emergence of vancomycin resistance in enterococci, therapeutic problems were extended beyond the inability to kill enterococci to the inability to inhibit them with commercially available antibiotics. Unfortunately, vancomycin resistance has predominated in strains of *Enterococcus faecium*, which have now increased in frequency in nosocomial infections due to this resistance. Although *E. faecium* found in normal individuals, including VRE from Europeans and from animals, are often susceptible to ampicillin, VRE from patients in U.S. and some European hospitals are *E. faecium* that are highly resistant to ampicillin, with MICs sometimes greater than 256  $\mu\text{g/ml}$ . Such strains are often resistant to many, if not all, commonly used antimicrobials. While chloramphenicol shows *in vitro* activity against a number of VRE, clinical efficacy and intolerability are issues. New compounds, quinupristin/dalfopristin and linezolid, were developed in part to address the problem of VRE. While

quinupristin/dalfopristin has the potential to display some bactericidal activity against enterococci, its killing activity is reduced in erythromycin resistant strains, a phenotype that predominates among VRE. Some multidrug combinations have appeared active *in vitro*, and some have been used *in vivo*, but currently the optimal therapy for serious infections caused by highly ampicillin resistant VRE remains unknown.

In addition to concerns about therapy of patients infected with VRE, enterococci are also known to share a number of resistance genes with other gram positive organisms such as staphylococci, pneumococci and other streptococci. In particular, the beta-lactamase gene widely present in *S. aureus* has been found in some isolates of *E. faecalis*, and both these genera share the *aac(6')/aph(2'')* gentamicin resistance gene, among others. Concern about the ability of enterococci to transfer their vancomycin resistance genes to staphylococci has come to fruition with the recent description of two separate vancomycin resistant *S. aureus* isolates with the *vanA* gene, the source of which in one patient was the patient's *vanA* containing *E. faecalis* isolate which could also transfer this resistance to *S. aureus in vitro*. It is likely that the role of VRE as a reservoir and source of vancomycin resistance genes for other staphylococci and other gram positive organisms will increase in the future.