valve replacement may need to be considered in the treatment of endocarditis caused by multidrug-resistant enterococci. Less severe infections are often related to indwelling intravascular catheters; removal of the catheter increases the likelihood of enterococcal eradication by a subsequent short course of appropriate antimicrobial therapy.

CHOICE OF ANTIMICROBIAL AGENTS

Among the β-lactams, the most active are the aminopenicillins (ampicillin, amoxicillin) and ureidopenicillins (i.e., piperacillin); next most active are penicillin G and imipenem. For *E. faecium*, a combination of high-dose ampicillin (up to 30 g/d) plus an aminoglycoside has been suggested—even for ampicillin-resistant strains if the MIC is ≤64 μg/mL—because a plasma ampicillin concentration of >100 μg/mL can be achieved at high doses. The only two aminoglycosides recommended for synergistic therapy in severe enterococcal infections are gentamicin and streptomycin. The use of amikacin is discouraged, tobramycin should never be used against *E. faecium*, and aminoglycoside monotherapy is not effective. Vancomycin is an alternative to β-lactam drugs for the treatment of *E. faecalis* infections but is less useful against *E. faecium* because resistance is common.

As mentioned above, use of the aminoglycoside–ampicillin combination for *E. faecalis* infections has become increasingly problematic because of toxicity in critically ill patients and increased rates of high-level resistance to aminoglycosides. A recent observational, nonrandomized, comparative study encompassing a multicenter cohort was conducted in 17 Spanish hospitals and 1 Italian hospital; this study found that the combination of ampicillin and ceftriaxone is as effective as ampicillin plus gentamicin in the treatment of *E. faecalis* endocarditis, with less risk of toxicity. Therefore, this regimen should be considered in patients at risk for aminoglycoside toxicity and could be considered for all patients.

Linezolid and quinupristin/dalfopristin (Q/D) are two agents approved by the U.S. Food and Drug Administration (FDA) for the treatment of some VRE infections (Table 174–2). Linezolid is not bactericidal, and its use in severe endovascular infections has produced mixed results; therefore, it is recommended only as an alternative to other agents. In addition, linezolid may cause significant toxicities (thrombocytopenia, peripheral neuropathy, and optic neuritis) when used in regimens given for >2 weeks. Nonetheless, linezolid may play a role in the treatment of enterococcal meningitis and other CNS infections, although clinical data are limited. Q/D is not active against most *E. faecalis* isolates, and its in vivo efficacy against *E. faecium* may often be compromised by resistance (see below). Adverse reactions to Q/D are common, including pain and inflammation at the infusion site and severe arthralgias and myalgias leading to discontinuation of treatment. Thus, Q/D should be used with caution and probably combined with other agents (Table 174–2).

The lipopeptide daptomycin is a bactericidal antibiotic with potent in vitro activity against all enterococci. Although daptomycin is not approved by the FDA for the treatment of VRE or *E. faecium* infections, it has been used alone (at high dosage) or in combination with other agents (ampicillin, ceftaroline, and tigecycline) with apparent success against multidrug-resistant enterococcal infections (Tables 174–1 and 174–2). The main adverse reactions to daptomycin are elevated creatine phosphokinase levels and eosinophilic pneumonitis (rare). Daptomycin is not useful against pulmonary infections because the pulmonary surfactant inhibits its antibacterial activity. Although the glycylcycline drug tigecycline is active in vitro against all enterococci (regardless of the isolates' vancomycin susceptibility), its use as monotherapy for endovascular or severe enterococcal infections is not recommended because of low attainable blood levels. Telavancin, a lipoglycopeptide approved by the FDA for the treatment of skin and soft tissue infections as well as hospital-associated pneumonia, is active against vancomycin-susceptible enterococci but not VRE. Oritavancin, a compound of the same class that is active against VRE, has recently been approved by the FDA for the treatment of bacterial skin and soft tissue infections and may offer promise for the treatment of VRE in the future.

ANTIMICROBIAL RESISTANCE

As mentioned above, resistance to β-lactam agents continues to be observed only infrequently in *E. faecalis*, although rare outbreaks caused by β-lactamase-producing isolates have occurred in the United States and Argentina. However, ampicillin resistance is common in *E. faecium*. The mechanism of this resistance is related to a penicillin-binding protein (PBP) designated PBP5, which is the target of β-lactam antibiotics. PBP5 exhibits lower affinity for ampicillin and can synthesize cell wall in the presence of this antibiotic, even when other PBPs are inhibited. Two common mechanisms of high-level ampicillin resistance (MIC, >64 μg/mL) in clinical strains are (1) mutations in the PBP5-encoding gene that further decrease the protein's affinity for ampicillin and (2) hyperproduction of PBP5. These factors preclude the use of all β-lactam agents in the treatment of *E. faecium* infections.

Vancomycin is a glycopeptide antibiotic that inhibits cell wall peptidoglycan synthesis in susceptible enterococci and has been widely used against enterococcal infections in clinical practice when the utility of β-lactams is limited by resistance, allergy, or adverse reactions. This effect is mediated by binding of the antibiotic to peptidoglycan precursors (UDP-MurNAc-pentapeptides) upon their exit from the bacterial cell cytoplasm. The interaction of vancomycin with the peptidoglycan is specific and involves the last two D-alanine residues of the precursor. The first isolates of VRE were documented in 1986, and vancomycin resistance (particularly in *E. faecium*) has since increased considerably around the world. The mechanism involves the replacement of the last D-alanine residue of peptidoglycan precursors with D-lactate or D-serine, with consequent high- and low-level resistance, respectively. There is significant heterogeneity among isolates, but either substitution substantially decreases the affinity of vancomycin for the peptidoglycan; with the D-lactate substitution, the MIC is increased by up to 1000-fold. Vancomycin-resistant organisms also produce enzymes that destroy the D-alanine-D-alanine ending precursors, ensuring that additional binding sites for vancomycin are not available.

High-level resistance to aminoglycosides (of which gentamicin and streptomycin are the only two tested by clinical laboratories) abolishes the synergism observed between cell wall–active agents and the aminoglycoside. This important phenotype is routinely sought in isolates from serious infections (Tables 174–1 and 174–2). The laboratory reports high-level resistance as gentamicin and streptomycin MICs of >500 μg/mL and >2000 μg/mL, respectively (agar dilution method) or as "SYN-R" (resistance to synergism). Genes encoding aminoglycoside-modifying enzymes are usually the cause of high-level resistance to these compounds and are widely disseminated among enterococci, decreasing the options for the treatment of severe enterococcal infections. The aforementioned enterococcal resistance to newer antibiotics such as linezolid (usually due to mutations in the 23S rRNA genes and the presence of an rRNA methylase), Q/D, daptomycin (involving major changes in cell membrane homeostasis), and tigecycline further reduces therapeutic alternatives.