Antibiotics for Gram-Positive Bacterial Infections: Vancomycin, Teicoplanin, Quinupristin/Dalfopristin, Oxazolidinones, Daptomycin, Dalbavancin, and Telavancin

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VANCOMYCIN

Vancomycin is a glycopeptide antibiotic that was isolated in 1956 from the actinomycete *Streptomyces orientalis*. It consists of a seven-membered peptide chain and two sugar moieties, vancosamine and glucose.[1] The clinical use of vancomycin became widespread in 1958 with the emergence of penicillinase-producing staphylococci, but the drug fell into disuse 2 years later with the advent of methicillin. Early

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preparations of vancomycin contained fermentation byproducts, resulting in marked toxicity. It is one of most widely used antibiotics in the United States for the treatment of serious gram-positive infections, particularly those involving methicillin-resistant Staphylococcus aureus (MRSA).[2]

Mechanism of Action

Vancomycin exhibits concentration-independent bactericidal activity by the inhibition of bacterial cell wall synthesis. Specifically, it complexes with the D-alanyl-D-alanine portion of peptide precursor units, inhibiting peptidoglycan polymerase and transpeptidation reactions. This prevents the cross-linking of the cell wall peptidoglycan, which occurs during the second stage of cell wall synthesis. Because β-lactams inhibit cell wall biosynthesis in the third phase, there is no cross-resistance between the drugs and no competition for binding sites. Like penicillin, vancomycin requires actively growing bacteria to exert its effect. Also, vancomycin is capable of injuring protoplasts by altering the permeability of their cytoplasmic membrane and selectively inhibiting RNA synthesis.[3,4] Vancomycin exhibits minimal concentration-dependent killing action, but a moderately long in vitro postantibiotic effect.[5]

Antimicrobial Activity

Virtually all *Staphylococcus aureus* strains are susceptible to vancomycin. In addition, the vast majority of coagulase-negative staphylococci are susceptible. Vancomycin-resistant enterococci (VRE) bloodstream isolates have increased over the years, and in 2002, 17.7% of all enterococci isolates were resistant to vancomycin. Vancomycin resistance was more frequent among *Enterococcus faecium* isolates, at 60.9%, whereas in the more frequently isolated *E. faecalis*, resistance was detected in only 2.5% of cases.[6]

Vancomycin is bactericidal for most gram-positive organisms, with minimum inhibitory concentrations (MICs) in the range of 1 to 4 μg/mL.[2] However, against enterococci, vancomycin is only bacteriostatic.

Vancomycin-aminoglycoside combinations are synergistic for the majority of *Staphylococcus aureus* strains, whether they are methicillin susceptible or methicillin resistant.[7] In addition, substantial improvements in cure rates for *Staphylococcus epidermidis* prosthetic valve endocarditis are achieved by adding rifampin, gentamicin, or both to vancomycin.[8] Barring the presence of high-level gentamicin-resistant isolates (MIC > 500 μg/mL), the combination of vancomycin-gentamicin is also synergistic for enterococci.

Vancomycin is bactericidal against a variety of other gram-positive aerobic and anaerobic organisms, including *Corynebacterium* spp, *Bacillus* spp, pneumococci, viridans streptococci, and clostridia, including *Clostridium difficile*. Most *Listeria* monocytogenes, lactobacilli, actinomycetes, and anaerobic streptococci are also susceptible.

Leuconostoc and *Pediococcus species*, which cause serious infections in immunocompromised patients, are resistant to vancomycin. Vancomycin has no activity against gram-negative organisms.

Pharmacokinetics, Dosing, and Administration

The 24-hour area under the curve (AUC)-MIC ratio is probably the most important pharmacokinetic (PK)-pharmacodynamic (PD) parameter correlating with the efficacy of vancomycin.[9] Vancomycin has a large volume of distribution, with therapeutic levels achievable in ascitic, pericardial, pleural, and synovial fluids. Vancomycin penetrates poorly into the aqueous humor and bile. Penetration into cerebrospinal fluid is poor,